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(71) Applicant: COR THERAPEUTICS, INC. [US/US]; 256
E. Grand Avenue, South San Francisco, CA 94080 (US).

(72) Inventors: ZHU, Bing-Yan; 3325 Adelaide Way, Belmont, CA 94002 (US). SCARBOROUGH, Robert, M.; 22 Greenbrier Court, Half Moon Bay, CA 94019 (US). WANG, Lingyan; 224 Brentwood Drive, South San Francisco, CA 94080 (US).

(74) Agent: LEE, Christine, S.; Morgan, Lewis & Bockius LLP, 1800 M. Street, N.W., Washington, DC 20036-5869 (US).

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(54) Title: INHIBITORS OF FACTOR Xa

(57) Abstract: Novel compounds, their salts and compositions related thereto having activity against mammalian factor Xa are disclosed. The compounds are useful *in vitro* or *in vivo* for preventing or treating coagulation disorders.

WO 00/71516 A2

INHIBITORS OF FACTOR Xa

Related Applications

This application claims benefit of priority under 35 USC § 119(e) to U.S.
5 Provisional Application No. 60/135,838 filed on May 24, 1999, which is herein
incorporated in its entirety by reference.

Field of the Invention

This invention relates to novel compounds which are potent and highly
selective inhibitors of isolated factor Xa or when assembled in the prothrombinase
10 complex. These compounds show selectivity for factor Xa versus other proteases of
the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g.
plasminogen activators, plasmin). In another aspect, the present invention relates to
novel monoamidino-containing compounds, their pharmaceutically acceptable salts,
and pharmaceutically acceptable compositions thereof which are useful as potent
15 and specific inhibitors of blood coagulation in mammals. In yet another aspect, the
invention relates to methods for using these inhibitors as therapeutic agents for
disease states in mammals characterized by coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the
20 physiological properties of vasoconstriction and coagulation. This invention is
particularly concerned with blood coagulation and ways in which it assists in
maintaining the integrity of mammalian circulation after injury, inflammation,
disease, congenital defect, dysfunction or other disruption. Although platelets and
blood coagulation are both involved in thrombus formation, certain components of
25 the coagulation cascade are primarily responsible for the amplification or
acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in
hemostasis. Thrombin plays a central role in thrombosis through its ability to
catalyze the conversion of fibrinogen into fibrin and through its potent platelet
30 activation activity. Direct or indirect inhibition of thrombin activity has been the
focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G.,
"Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin

and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. **5**, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

- 5 A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active
- 10 substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* **15**, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has
- 15 been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see e.g., WO 94/13693.

- Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent
- 20 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", *J. Biol. Chem.*, **263**, 10162-10167 (1988). Another potent and
- 25 highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithodoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" *Science*, **248**, 593-596 (1990).

- Factor Xa inhibitory compounds which are not large polypeptide-type
- 30 inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", *Thromb. Res.*, **19**, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", *Biochemistry*, **25**, 4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic

Protease Inhibitor (FUT-175) on the Coagulation System", *Haemostasis*, **15**, 164-168 (1985); Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", *Thromb. Res.*, **54**, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", *Biochemistry*, **27**, 2547-2557 (1988); Hauptmann, J. *et al.*, "Comparison of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", *Thromb. Haemost.*, **63**, 220-223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)-NH₂ group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naphthyl group via a straight or branched chain alkylene, -C(=O) or -S(=O)₂ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds that have different combinations of bridging groups and functional groups than compounds previously discovered are needed, particularly compounds which selectively or preferentially bind to Factor Xa. Compounds with a higher degree of binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability and/or solubility.

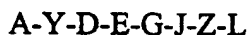
Summary of the Invention

The present invention relates to novel compounds which inhibit factor Xa,

their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

In a preferred embodiment, the present invention provides a compound of the formula I:



wherein:

A is selected from:

- (a) C_1 - C_6 -alkyl;
- (b) C_3 - C_8 -cycloalkyl;
- (c) $-NR_2R_3$, $R_3C(=NR_2)-$, $R_2R_3N-C(=NR_2)-$, $R_2R_3N-C(=NR_2)-N(R_3)-$
- (d) phenyl, which is independently substituted with 0-2 R^1 substituents;
- (e) naphthyl, which is independently substituted with 0-2 R^1 substituents; and
- (f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^1 substituents;

R¹ is selected from:

5 Halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, R²C(=NR³)-, R²R³N-C(=NR²)-, (CH₂)_mNR²R³, CONR²R³, SO₂NR²R³, SO₂R², CF₃, OR², and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, -CN C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

10 R² and R³ are independently selected from the group consisting of:

15 H, OR², NR²R³, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂; R² and R³ together can form 3-8 membered cycloalkyl or heterocyclic systems.

m is an integer of 0-2;

Y is a member selected from the group consisting of:

20 a direct link, -CH₂-, -C(=O)-, -N(R⁴)-, -N(R⁴)CH₂-, -C=N(R⁴)-, -C(=O)-N(R⁴)-, -N(R⁴)-C(=O)-, -SO₂-, -O-, -SO₂-N(R⁴)- and -N(R⁴)-SO₂-;

R⁴ is selected from:

25 H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

D is a direct link or is a member selected from the group consisting of:

- 30 (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;
 (b) direct link

- (c) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and
- (d) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

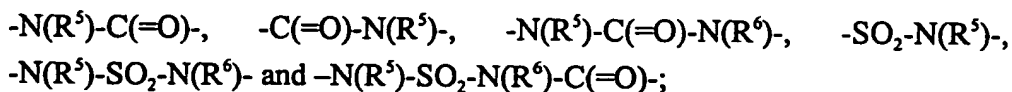
R^{1a} is selected from:

- Halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl C_{3-8} cycloalkyl, -CN, -NO₂, $(CH_2)_mNR^{2a}R^{3a}$, $CONR^{2a}R^{3a}$, $SO_2NR^{2a}R^{3a}$, SO_2R^{2a} , CF₃, OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl C_{3-8} cycloalkyl, -CN and -NO₂;

- R^{2a} and R^{3a} are independently selected from the group consisting of:

- H, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl C_{3-8} cycloalkyl, C_{0-4} alkylphenyl and C_{0-4} alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl C_{3-8} cycloalkyl, -CN and -NO₂;

E is a member selected from the group consisting of:



- R^5 and R^6 are independently selected from:

- H, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl C_{3-8} cycloalkyl, C_{0-4} alkylphenyl, C_{0-4} alkylnaphthyl, C_{0-4} alkylheteroaryl, C_{1-4} alkylCOOH and C_{1-4} alkylCOOC₁₋₄alkyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl, naphthyl and heteroaryl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4} alkyl,

C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl C_{3-8} cycloalkyl, -CN and -NO₂;

G is a member selected from the group consisting of:

a direct link, -CR⁷R⁸- and -CR^{7a}R^{8a}-CR^{7b}R^{8b}-

- 5 wherein R⁷, R⁸, R^{7a}, R^{8a}, R^{7b} and R^{8b} are independently a member selected from from the group consisting of:

- hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl- C_{3-8} cycloalkyl, C_{0-4} alkylphenyl, C_{0-4} alkylnaphthyl, -OR⁹, - C_{0-4} alkylCOOR⁹,
 10 - C_{0-4} alkylC(=O)NR⁹R¹⁰, - C_{0-4} alkylC(=O)NR⁹-CH₂-CH₂-O-R¹⁰,
 - C_{0-4} alkylC(=O)NR⁹(-CH₂-CH₂-O-R¹⁰)-₂, -N(R⁹)COR¹⁰, -N(R⁹)C(=O)R¹⁰,
 -N(R⁹)SO₂R¹⁰, and a naturally occurring or synthetic amino acid side chain,
 wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and
 naphthyl moieties may be independently replaced with a member selected
 from the group consisting of halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8}
 15 $cycloalkyl$, C_{0-4} alkyl- C_{3-8} cycloalkyl, -CN and -NO₂;

R⁹ and R¹⁰ are independently selected from:

- H, C_{1-4} alkyl, C_{0-4} alkylphenyl and C_{0-4} alkylnaphthyl, wherein from 1-4
 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may
 be independently replaced with a member selected from the group consisting
 20 of halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl- C_{3-8}
 $cycloalkyl$, -CN and -NO₂, and wherein R⁹ and R¹⁰ taken together can form a
 5-8 membered heterocyclic ring;

J is a member selected from the group consisting of:



- 25 wherein the ring carbons or second ring nitrogen of the amino ring structure and/or the ring carbons on the alkylene bridging groups attached to the amino ring structure may be independently substituted by a total of 0 to 4 R¹¹, R^{11a}, R^{11b} and R^{11c} groups;

R¹¹, R^{11a}, R^{11b} and R^{11c} are independently a member selected from the group consisting of:

hydrogen, -OH, -O-C₁₋₄alkyl, -C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkyl-C₃₋₈cycloalkyl, C₀₋₄alkylphenyl, C₀₋₄alkylnaphthyl, C₀₋₄alkylheterocyclic ring having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S, CH₂COOC₁₋₄alkyl, CH₂COOC₁₋₄alkylphenyl and CH₂COOC₁₋₄alkylnaphthyl;

Z is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;
- (b) naphthyl, which is independently substituted with 0-2 R^{1b} substituents; and
- (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

- Halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, NR^{2b}R^{3b}, -CH₂NR^{2b}R^{3b}, CONR^{2b}R^{3b}, SO₂NR^{2b}R^{3b}, SO₂R^{2b}, CF₃, OR^{2b}, O-CH₂-CH₂-OR^{2b}, O-CH₂-COOR^{2b}, N(R^{2b})-CH₂-CH₂-OR^{2b}, N(-CH₂-CH₂-OR^{2b})₂, N(R^{2b})-C(=O)R^{3b}, N(R^{2b})-SO₂-R^{3b}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

R^{2b} and R^{3b} are independently selected from the group consisting of:

- H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

L is selected from:

H, -CN, $C(=O)NR^{12}R^{13}$, $(CH_2)_nNR^{12}R^{13}$, $C(=NR^{12})NR^{12}R^{13}$, $NR^{12}R^{13}$, OR^{12} , $-NR^{12}C(=NR^{12})NR^{12}R^{13}$, and $NR^{12}C(=NR^{12})-R^{13}$;

R^{12} and R^{13} are independently selected from:

5 hydrogen, $-OR^{14}$, $-NR^{14}R^{15}$, $C_{1-4}alkyl$, $C_{0-4}alkylphenyl$, $C_{0-4}alkylnaphthyl$, $COOC_{1-4}alkyl$, $COO-C_{0-4}alkylphenyl$ and $COO-C_{0-4}alkylnaphthyl$, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, $C_{1-4}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{3-8}cycloalkyl$, $C_{0-4}alkylC_{3-8}cycloalkyl$, -CN, and $-NO_2$;

10 R^{14} and R^{15} are independently selected from:

H, $C_{1-4}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{3-8}cycloalkyl$, $C_{0-4}alkylC_{3-8}cycloalkyl$, $C_{0-4}alkylphenyl$ and $C_{0-4}alkylnaphthyl$, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, $C_{1-4}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{3-8}cycloalkyl$, $C_{0-4}alkylC_{3-8}cycloalkyl$, -CN, and $-NO_2$;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In certain aspects of this invention, compounds are provided which are useful
 20 as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above compounds and pharmaceutical compositions for preventing or treating disease
 25 states characterized by undesired thrombosis or disorders of the blood coagulation process in mammals, or for preventing coagulation in biological samples such as, for example, stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic
 30 agent and/or an anticoagulant.

The preferred compounds also include their pharmaceutically acceptable isomers, hydrates, solvates, salts and prodrug derivatives.

Detailed Description of the Invention

Definitions

5 In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkynyl" (or "alkynyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkynyl each refer to radicals
10 having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon
15 atoms and preferably 3 to 7 carbon atoms.

As used herein, the terms "carbocyclic ring structure" and "C₃₋₁₆ carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of:
20 of: a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the
25 rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-
30 aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not

limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be
5 attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

10 The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to carbocyclic aryl,
15 heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, naphthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms
20 designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydrl, trityl, and the like, all of which may be optionally substituted.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is
25 intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected
30 from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms

present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless
5 indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring
10 systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of
15 the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single
20 heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more than 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocyclic and bicyclic heterocyclic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl,
25 benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indoliziny, indolyl, 3H-indolyl,
30 isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl,
35 phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl,

purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofurany, 5 tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, 10 pyridinyl, furany, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazoliny, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocyclic ring structures.

As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at 15 least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals 20 having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $-CH_2-$.

The term "pharmaceutically acceptable salts" includes salts of compounds 25 derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the 30 biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and

the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

5 "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts
10 of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine,
15 ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

 "Biological property" for the purposes herein means an *in vivo* effector or
20 antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or
25 any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

 In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein
30 may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric

carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

Preferred Embodiments

In a preferred embodiment, the present invention provides a compound
5 according to the formula I:



wherein:

A is selected from:

- 10 (a) $-NR^2R^3$, $R^3C(=NR^2)-$, $R^2R^3N-C(=NR^2)-$, $R^2R^3N-C(=NR^2)-N(R^3)-$
- (b) phenyl, which is independently substituted with 0-2 R^1 substituents;
- (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be
15 substituted with 0-2 R^1 substituents;

R^1 is selected from:

- halo, $R^2-C(=NR^3)-$, $R^2R^3N-C(=NR^2)-$, C_{1-4} alkyl, NO_2 , $-CN$, $(CH_2)_mNR^2R^3$, $CONR^2R^3$, $SO_2NR^2R^3$, SO_2R^2 , CF_3 , OR^2 , and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and
20 S;

R^2 and R^3 are independently selected from the group consisting of:

H, C_{1-4} alkyl and C_{0-4} alkylaryl,

m is an integer of 0-2;

Y is a member selected from the group consisting of:

- 25 a direct link, $-CH_2-$, $-C(=O)-$, $-N(R^4)-$, $-N(R^4)CH_2-$, and $-C=N(R^4)-$,

R^4 is selected from:

H, C_{1-4} alkyl and C_{0-4} alkylaryl;

D is absent or is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;
and
- (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

R^{1a} is selected from:

- Halo, C_{1-4} alkyl, -CN, -NO₂, $(CH_2)_mNR^{2a}R^{3a}$, $SO_2NR^{2a}R^{3a}$, SO_2R^{2a} , CF₃, OR^{2a}, and a 5-6 membered aromatic heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C_{1-4} alkyl and C_{0-4} alkylaryl;

E is a member selected from the group consisting of:

-N(R⁵)-C(=O)-, and -C(=O)-N(R⁵)-,

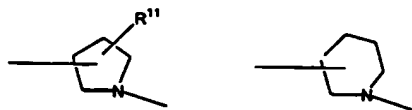
- 15 R^5 and R^6 are independently selected from:

H, C_{1-4} alkyl, C_{0-4} alkylaryl, C_{0-4} alkylheteroaryl, C_{1-4} alkylCOOH and C_{1-4} alkylCOOC₁₋₄alkyl;

G is a member selected from the group consisting of:

a direct link,

- 20 J is a member selected from the group consisting of:



- wherein the ring carbons or the second ring nitrogen of the amino ring structure and/or the ring carbons on the alkylene bridging groups attached to the amino ring structure may be independently substituted by a total of 0 to 4 R^{11} , R^{11a} , R^{11b} and R^{11c} groups;

R^{11} , R^{11a} , R^{11b} and R^{11c} are independently a member selected from the group consisting of:

- 5 hydrogen, -OH, -O- C_{1-4} alkyl, - C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl- C_{3-8} cycloalkyl, C_{0-4} alkylphenyl, C_{0-4} alkylnaphthyl, C_{0-4} alkylheterocyclic ring having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S, CH_2COOC_{1-4} alkyl, CH_2COOC_{1-4} alkylphenyl and CH_2COOC_{1-4} alkylnaphthyl;

Z is a member selected from the group consisting of:

- (a) aryl, which is independently substituted with 0-2 R^{1b} substituents; and
 10 (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

- 15 halo, C_{1-4} alkyl, -CN, -NO₂, $NR^{2b}R^{3b}$, $SO_2NR^{2b}R^{3b}$, SO_2R^{2b} , CF₃, OR^{2b} , O-CH₂-CH₂- OR^{2b} , O-CH₂-COOR^{2b}, $N(R^{2b})-CH_2-CH_2-OR^{2b}$, $N(-CH_2-CH_2-OR^{2b})_2$, $N(R^{2b})-C(=O)R^{3b}$, $N(R^{2b})-SO_2-R^{3b}$, and a 5-6 membered aromatic heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S;

R^{2b} and R^{3b} are independently selected from the group consisting of:

- 20 H, C_{1-4} alkyl and C_{0-4} alkylaryl;

L is selected from:

H, -CN, $C(=O)NR^{12}R^{13}$, $(CH_2)_nNR^{12}R^{13}$, $C(=NR^{12})NR^{12}R^{13}$, $NR^{12}R^{13}$, OR^{12} , $-NR^{12}C(=NR^{12})NR^{12}R^{13}$ and $NR^{12}C(=NR^{12})-R^{13}$;

R^{12} and R^{13} are independently selected from:

- 25 hydrogen, - OR^{14} , - $NR^{14}R^{15}$, C_{1-4} alkyl, C_{0-4} alkylaryl, $COOC_{1-4}$ alkyl, and $COO-C_{0-4}$ alkylaryl;

R^{14} and R^{15} are independently selected from:

H and C_{1-4} alkyl; and

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In a further preferred embodiment, the present invention provides a compound according to the formula I:

5 A-Y-D-E-G-J-Z-L

wherein:

A is selected from:

- (a) phenyl, which is independently substituted with 0-2 R¹ substituents;
- 10 (b) -NR₂R₃, R₃C(=NR₂)-, R₂R₃N-C(=NR₂)-, R₂R₃N-C(=NR₂)-N(R₃)- and
- (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R¹ substituents;

15 R¹ is selected from:

halo, R₂-C(=NR₃)-, R₂R₃N-C(=NR₂)-, (CH₂)_mNR²R³, SO₂NR²R³ and SO₂R²;

R² and R³ are independently selected from the group consisting of:

H and C₁₋₄alkyl;

20 Y is a member selected from the group consisting of:

a direct link, -C(=O)-, CH₂, C(=NH)-;

D is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents; and
- 25 (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are

selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

R^{1a} is selected from:

Halo and C₁₋₄alkyl;

5 R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C₁₋₄alkyl, C₀₋₄alkylaryl;

E is a member selected from the group consisting of:

-N(R⁵)-C(=O)- and -C(=O)-N(R⁵)-;

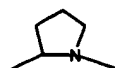
R⁵ and R⁶ are independently selected from:

10 H, C₁₋₄alkyl, C₀₋₄alkylaryl and C₀₋₄alkylheteroaryl;

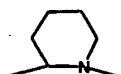
G is a member selected from the group consisting of:

a direct link,

J is a member selected from the group consisting of:



and



15

Z is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;
- (b) an aromatic heterocyclic ring having from 5 to 10 ring atoms, wherein 1-4 ring atoms are selected from N, O and S, and wherein the ring may be substituted independently by from 0-2 R^{1b} substituents; and
- (c) a fused aromatic bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, wherein the bicyclic ring system may be substituted with 0-2 R^{1b} substituents;
- 20
- 25

R^{1b} is selected from:

halo, C₁₋₄alkyl, OH, OBn, O-CH₂-CH₂-OH, O-CH₂-CH₂-OCH₃,
O-CH₂-COOH, O-CH₂-C(=O)-O-CH₃, NH₂, NH-CH₂-CH₂-O-CH₃,
NH-C(=O)-O-CH₃, and NH-SO₂-CH₃;

5 L is selected from:

H, C(=O)NR¹²R¹³, (CH₂)_nNR¹²R¹³ and C(=NR¹²)NR¹²R¹³;

R¹² and R¹³ are independently selected from:

hydrogen and C₁₋₄alkyl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and

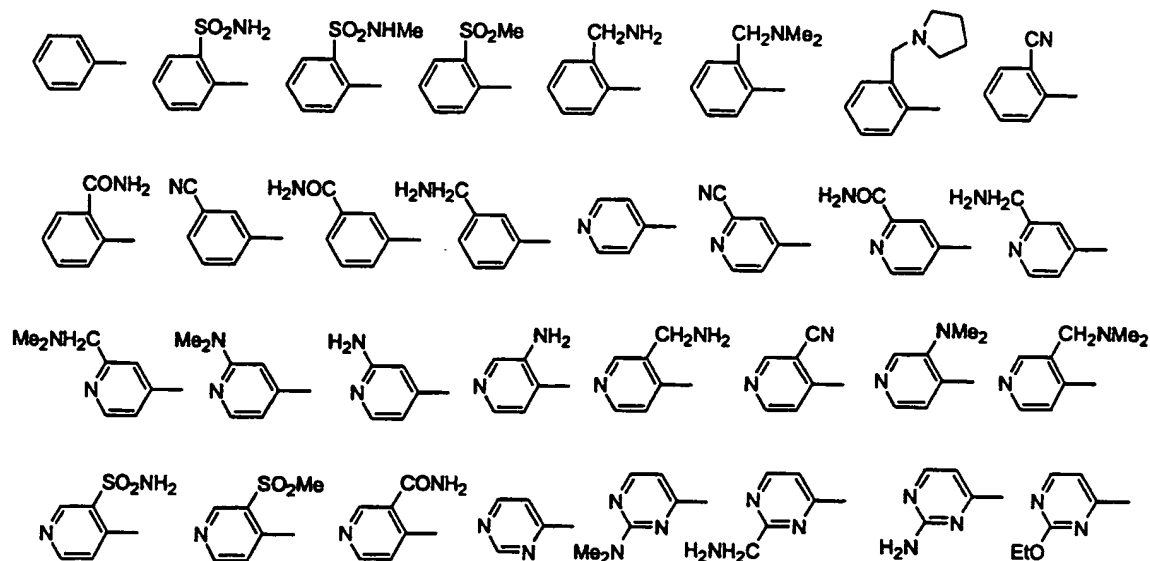
10 prodrug derivatives thereof.

In a further preferred embodiment, the present invention provides a
compound according to formula I:

A-Y-D-E-G-J-Z-L

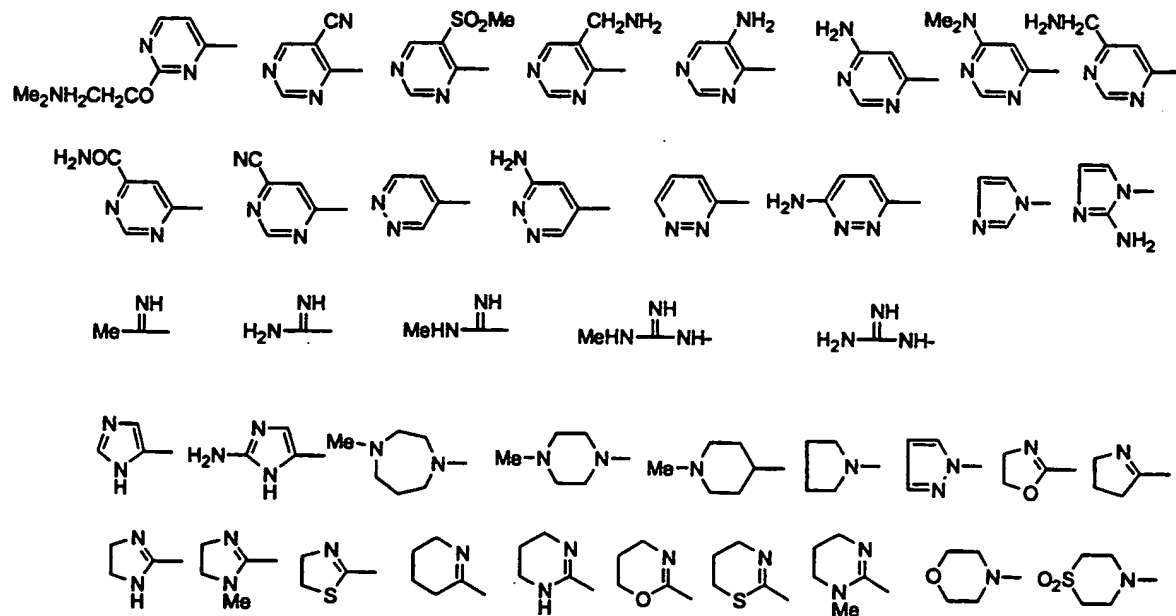
15 wherein

A is a member selected from the group consisting of:



5

A is also a member selected from the group consisting of:

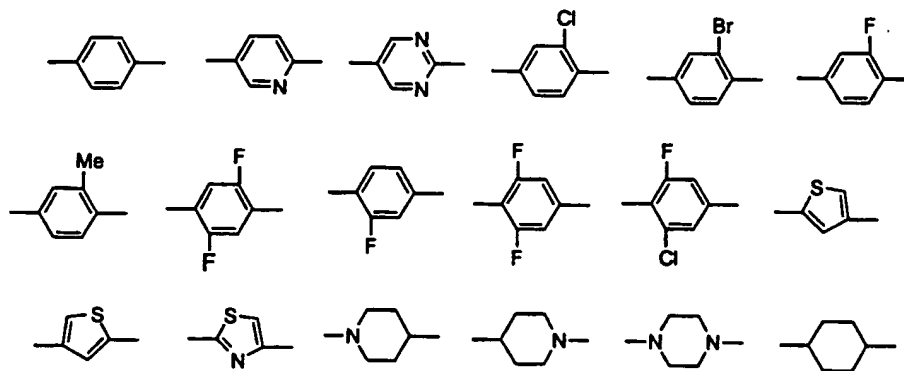


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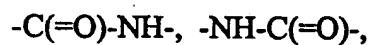
Y is selected from the group consisting of:

a direct link, -CO-, -N(Me)-, -N(Me)-CH₂-, CH₂-, C(=NH)-

D is a direct link or a member selected from the group consisting of:



5 E is a member selected from the group consisting of::



G is a member selected from the group consisting of:

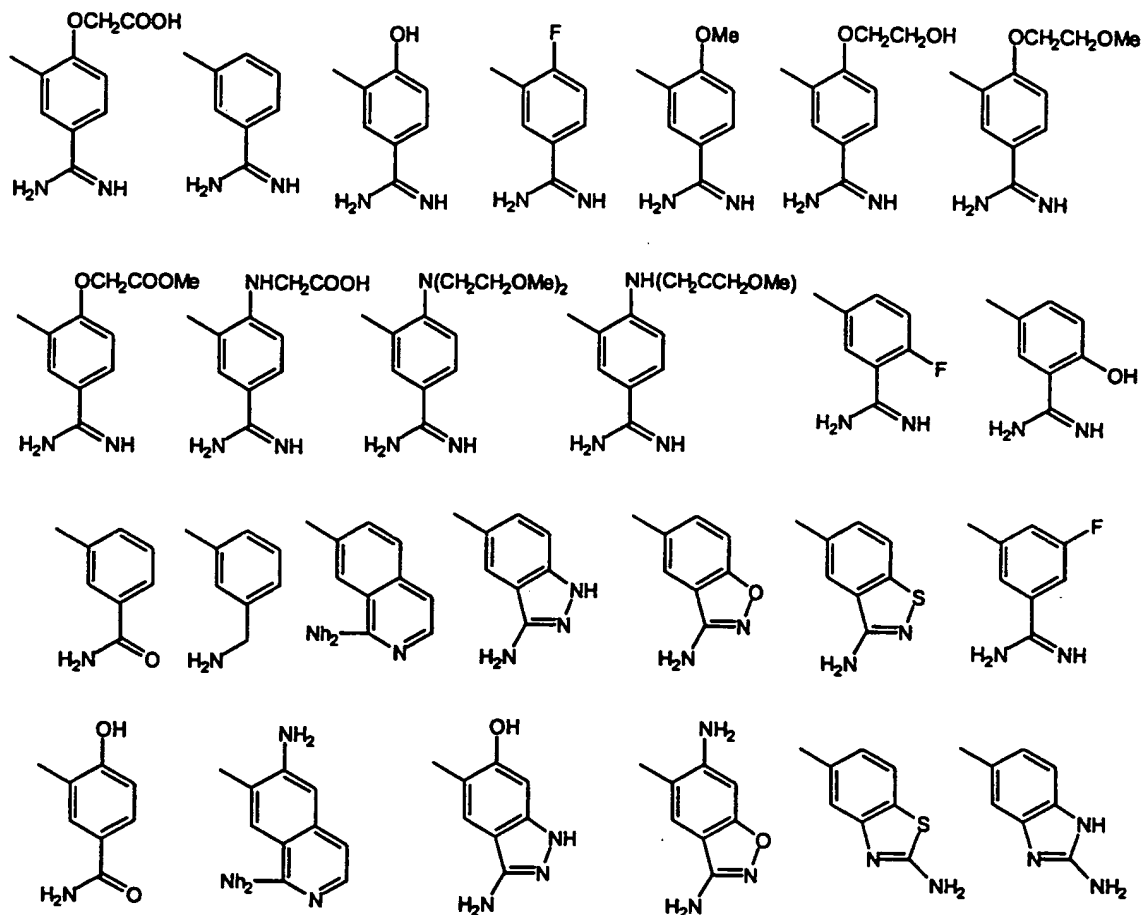
a direct link,

J is a member selected from the group consisting of:

10

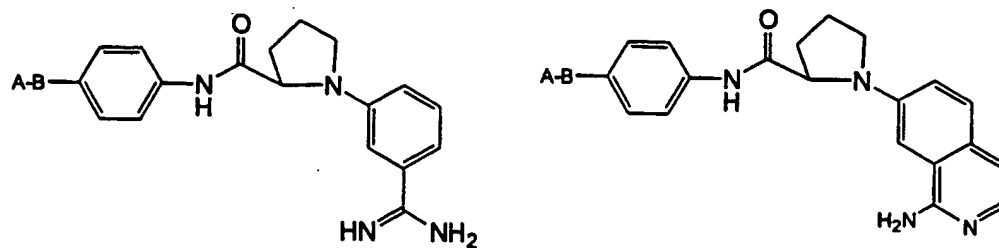


Z and L taken together are a member selected from the group consisting of:

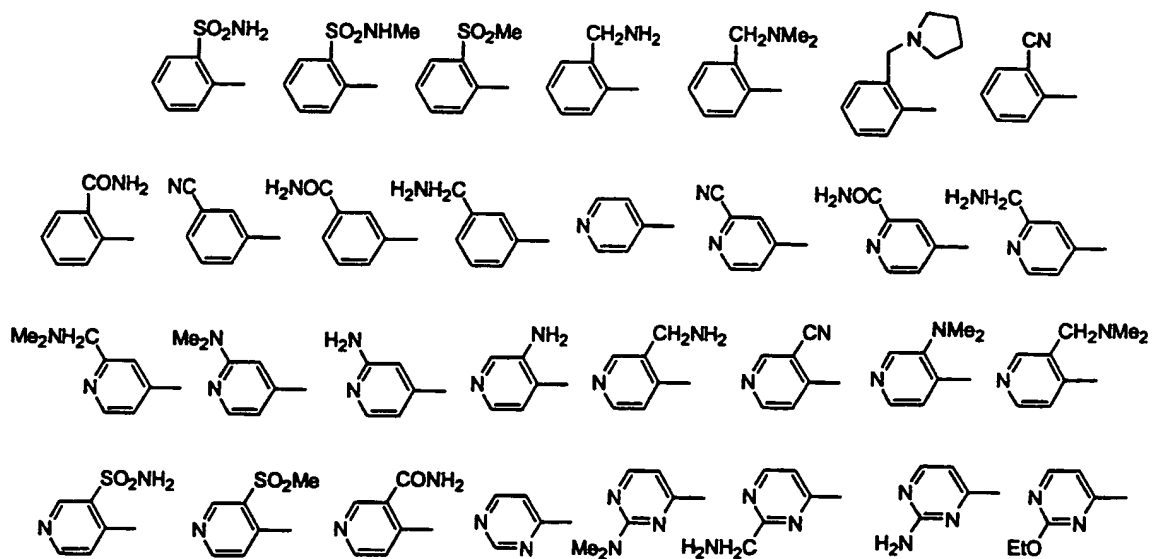


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and
5 prodrug derivatives thereof.

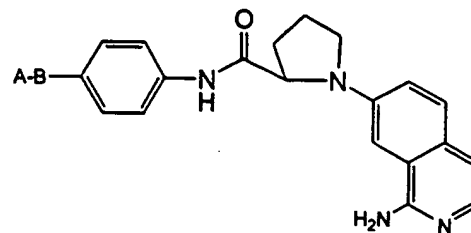
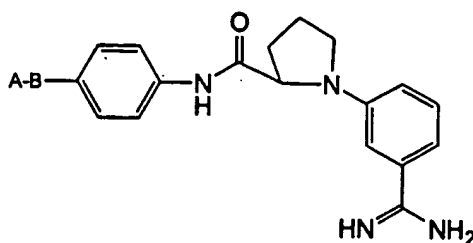
The following non-limiting tables illustrate representative compounds of the
present invention:



Where A-B is

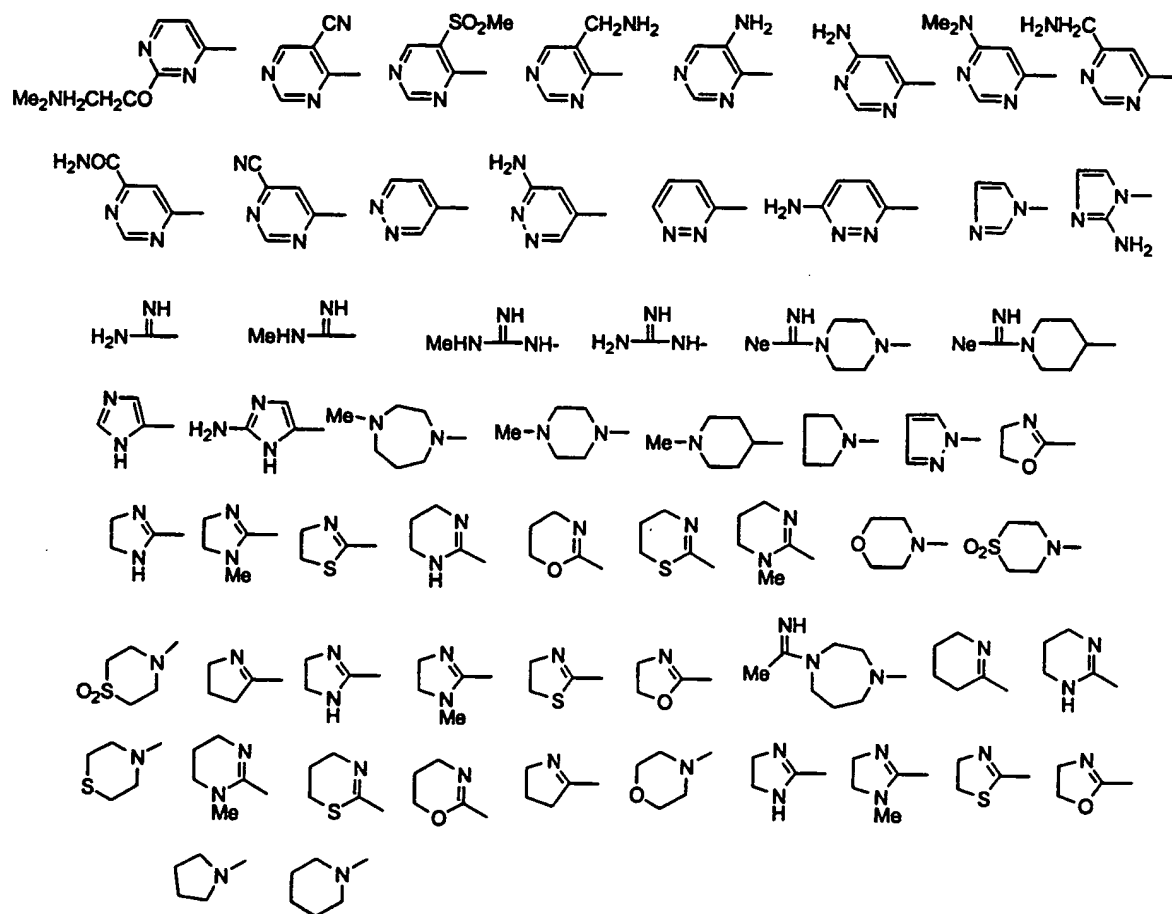


Compounds of the following structures:

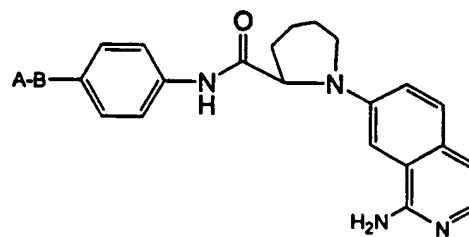
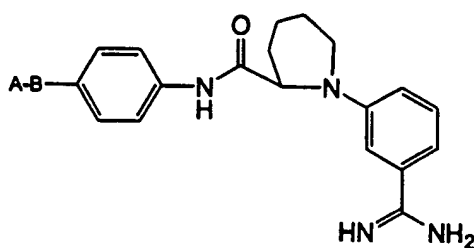


Where B is direct link, CH_2 , $-\text{CO}-$, $-\text{SO}_2$, $-\text{C}(=\text{NH})-$, $-\text{NH}-$, $-\text{N}(\text{Me})-$, $-\text{N}(\text{Me})\text{CH}_2-$.

A is selected from:

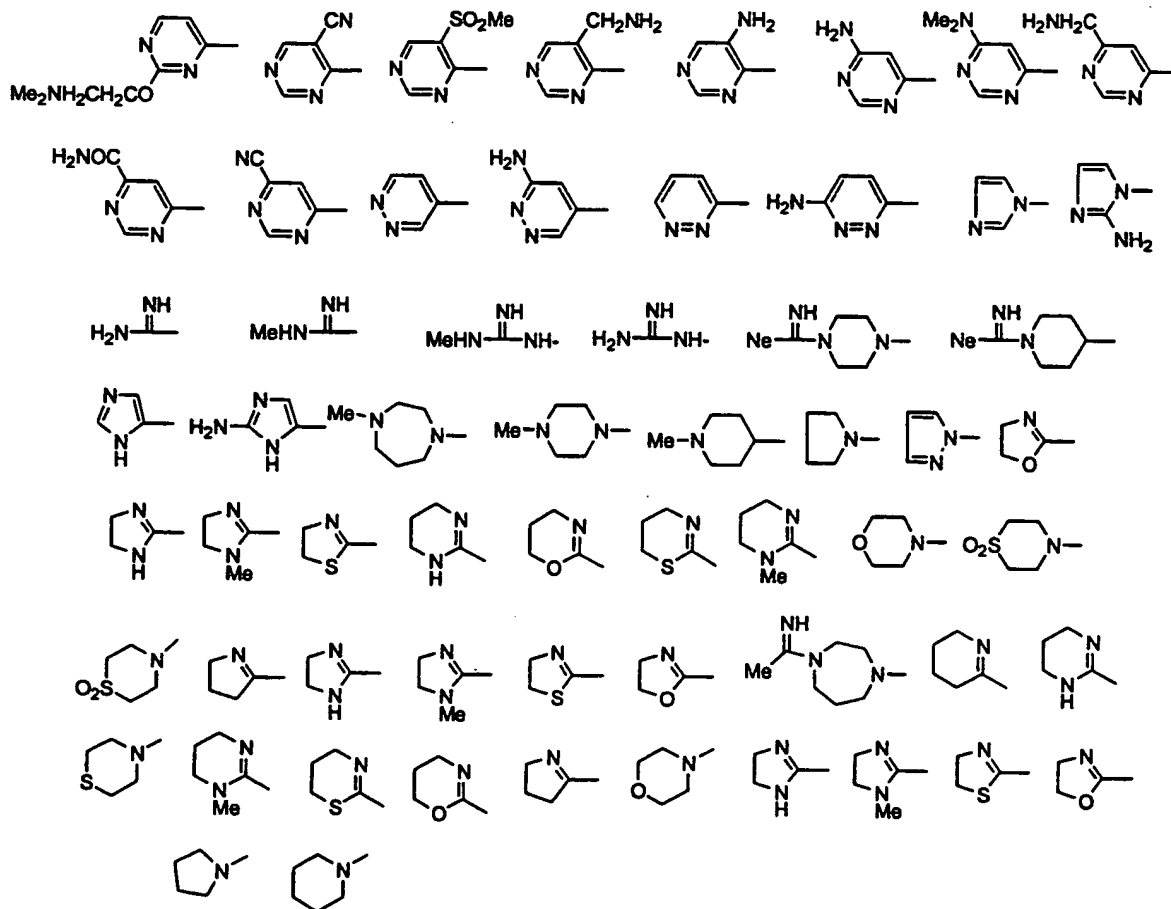


Compounds of the following structures:

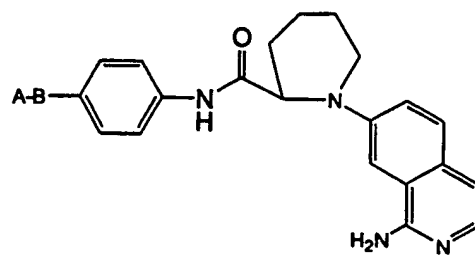
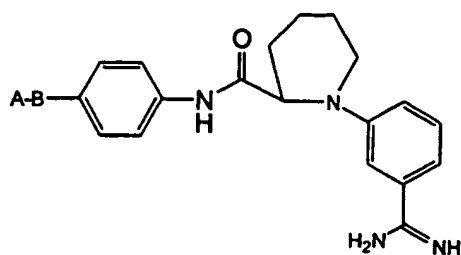


Where B is direct link, CH₂, -CO-, -SO₂-, C(=NH)-, -NH-, -N(Me)-, -N(Me)CH₂-

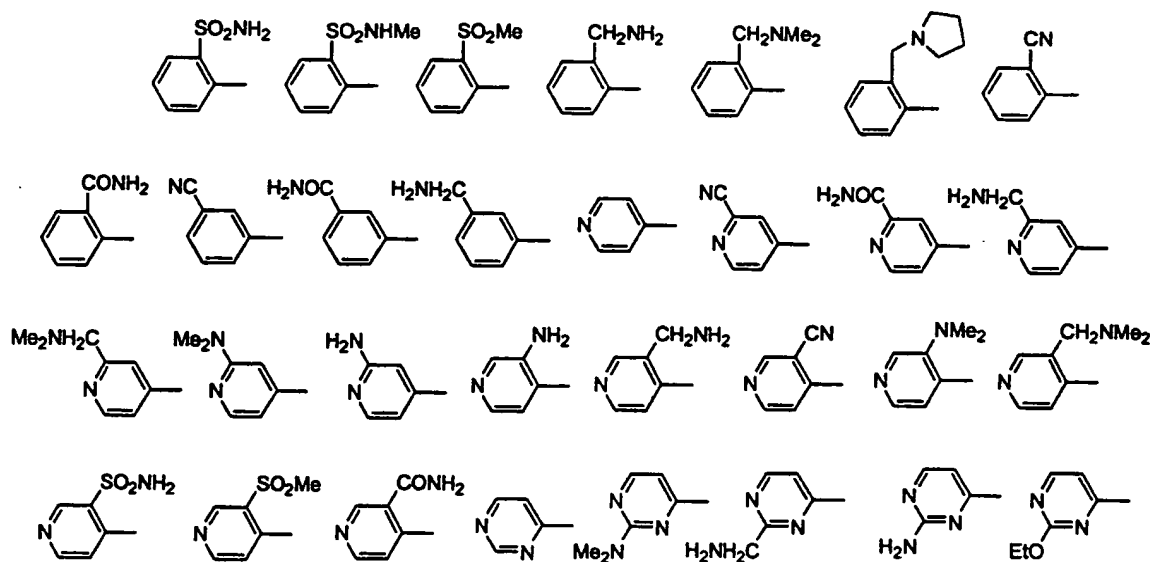
A is selected from:



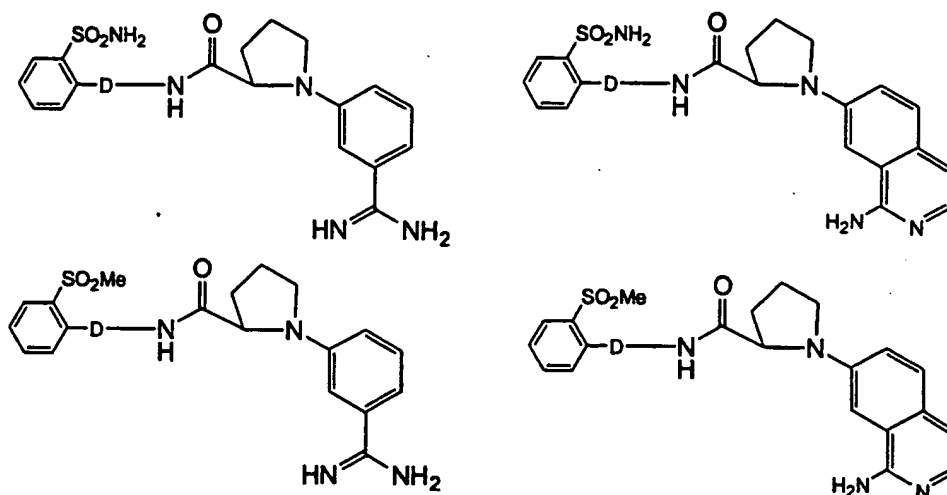
Compounds of the following formula:



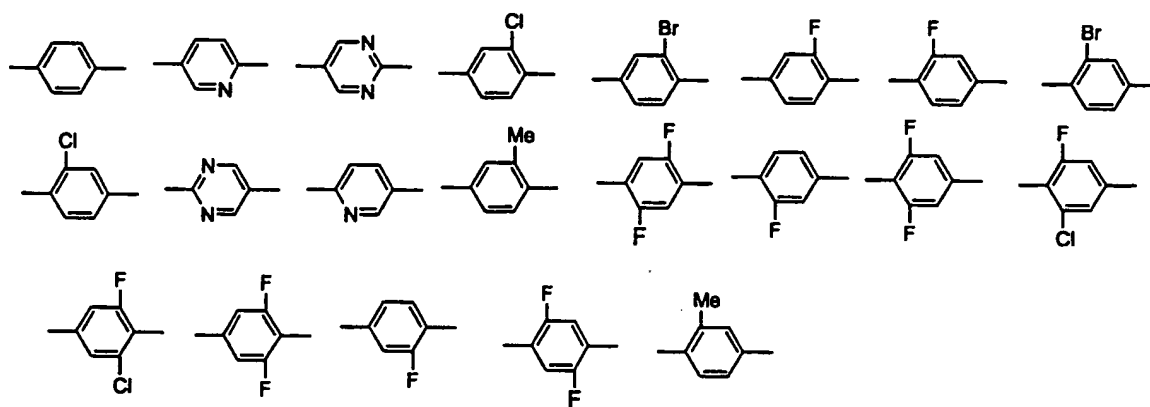
Where A-B is



The compounds of the following formula:



Where D is selected from



This invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates and solvates of the compounds of formulas I, II and III. In addition, the compounds of formulas I, II and III can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates and solvates of such isomers and tautomers.

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the

processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or
5 more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the
10 same general process.

Prodrug Derivatives of Compounds

This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either
15 spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug
20 compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp.
25 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent
30 acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

As mentioned above, the compounds of this invention find utility as

therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic
5 shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation
10 cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a
15 therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous
20 vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

25 The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the
30 compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the

present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as

polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrans, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium
5 and/or nonionic surfactants such as Tween, Pluronic or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or
10 as an aqueous solution. The pH of the preparations of this invention typically will be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as orally,
15 intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped
20 articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar
25 vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this
30 invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxypropyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers

useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block
5 copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

10

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration,
15 the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the
20 route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

25

The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a
30 single or 2 to 4 divided daily doses and/or continuous infusion.

30

Typically, about 5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical
35 practice. The amount of active ingredient in these compositions is such that a

suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Preparation of Compounds

The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See, Bodanszky, "The Principles of Peptide Synthesis", Hafner, *et al.*, Eds., Springer-Verlag, Berlin, 1984.

Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

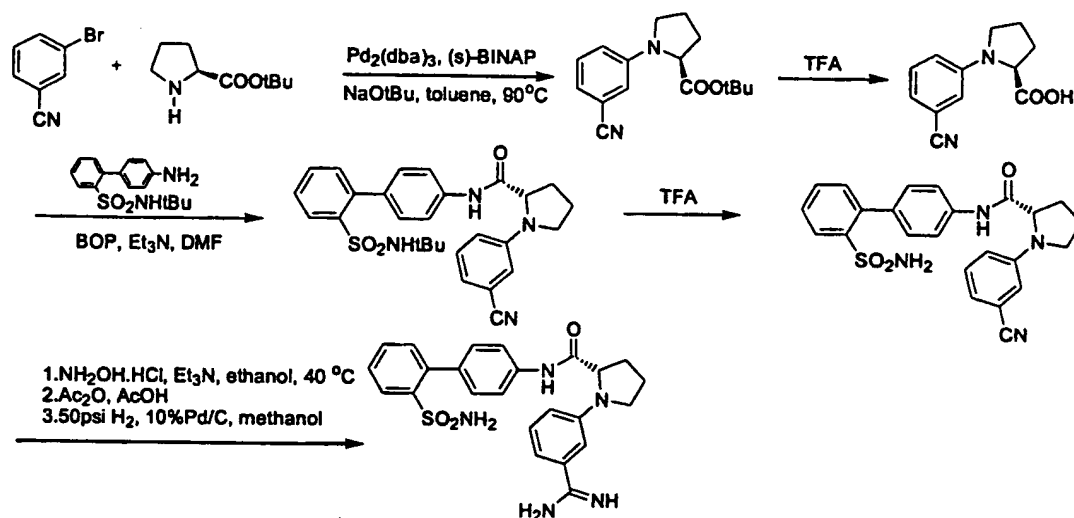
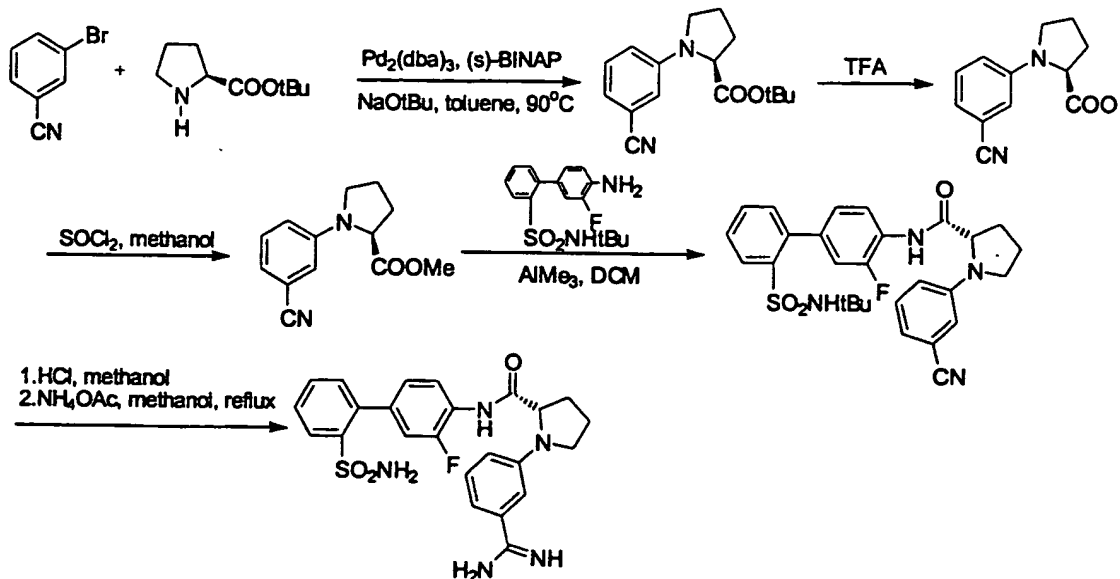
Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

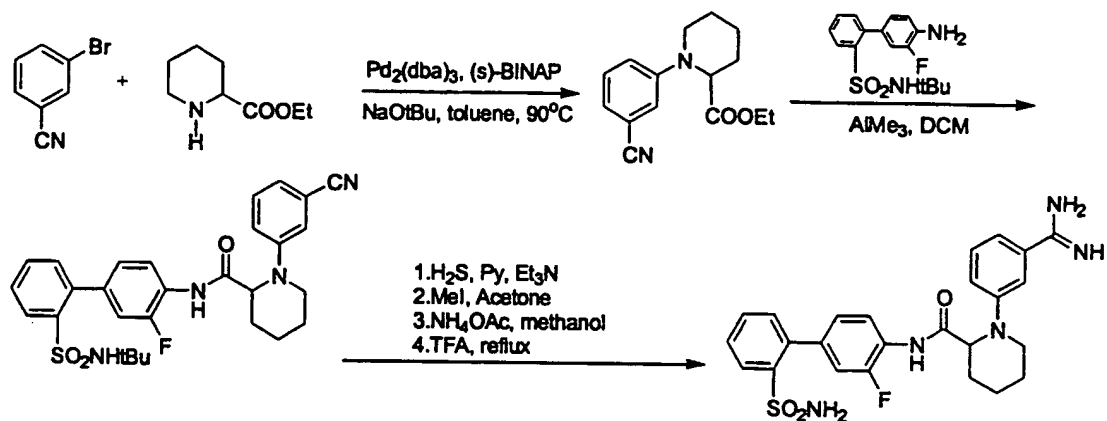
During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross reaction during the coupling procedure. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

Non-limiting exemplary synthesis schemes are outlined directly below, and

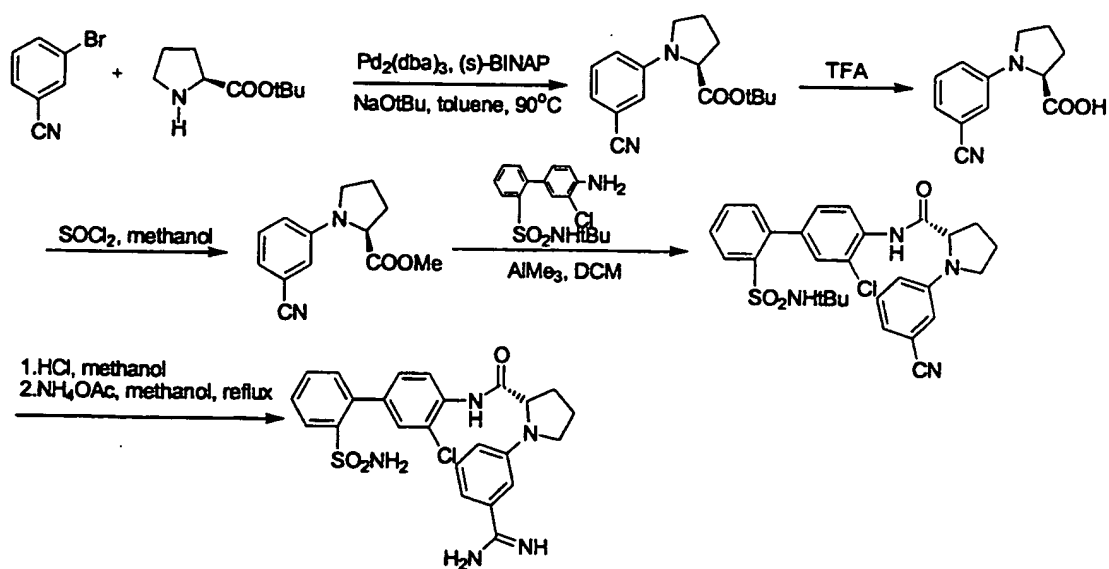
specific steps are described in the Examples. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

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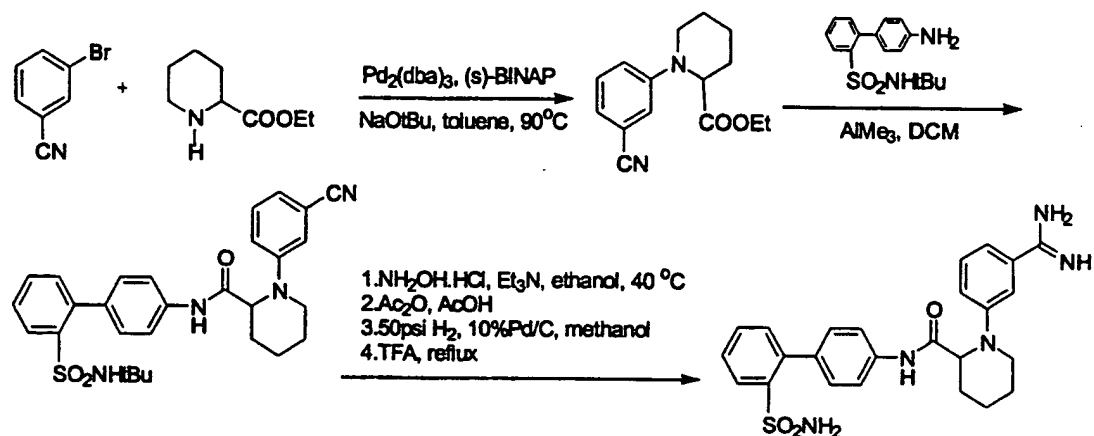
Scheme 1Scheme 2

Scheme 3

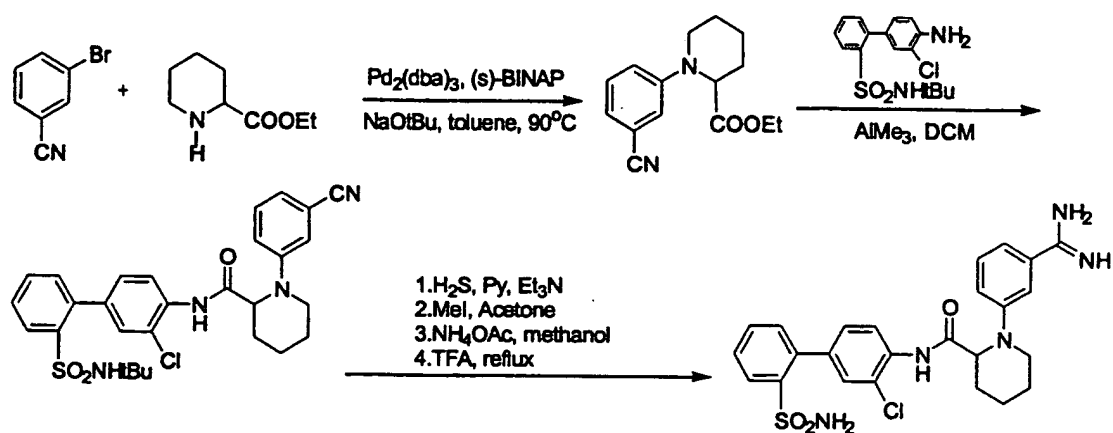
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Scheme 4

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Scheme 5

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Scheme 6

Compositions and Formulations

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts
5 are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or
10 more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the
15 same general process.

Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration,
20 suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal
25 being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrans, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronic or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a

variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as
5 biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of
10 lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers.
15 Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic
20 acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.
25 Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as

microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either

5 thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity

10 and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the

15 microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction,

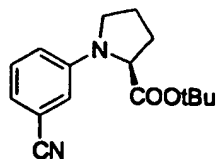
20 unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous

25 thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic

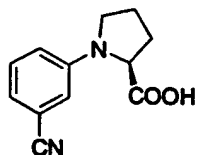
shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications
5 associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

10 Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material
15 such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

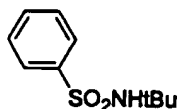
Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed
20 methods. The following working examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

EXAMPLESExample 1

- 5 To a solution of 3-bromobenzonitrile (2.73g, 15mmol), H(L)-Proline-OtBu (5.14g, 30mmol), sodium tert-butoxide (2.02g, 21mmol) and (s)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (186mg, 0.3mmol) in toluene (30ml) was added tris(dibenzylideneacetone)dipalladium (0) (137mg, 0.15mmol). The mixture was stirred at 90 °C for 6 hrs. After the filtration of the solid, the filtrate was
- 10 concentrated *in vacuo*. The residue was purified by silica gel column chromatography using solvent system 10% ethyl acetate in hexane as eluent to give the title compound as a light yellowish oil (336mg, 82%). ES-MS (M+H)⁺ = 273.

Example 2

- 15 The compound of example 1 (1.4g, 5.15mmol) was dissolved in trifluoroacetic acid (5ml). The mixture was stirred at room temperature for 5 hrs. The solvent was evaporated *in vacuo* to give the title compound (1.14g, 100%). ES-MS (M+H)⁺ =
- 20 217.

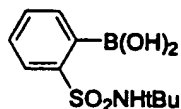
Example 3

- 25 To a solution of tert-butylamine (5.73g, 78.4mmol) and triethylamine (16.6ml, 119mmol) in dichloromethane (200ml) in an ice bath was added benzenesulfonyl chloride (13.85g, 78.4mmol) dropwise. The mixture was stirred at room temperature overnight. It was washed with saturated sodium carbonate (60ml) and brine (60ml).
- 30 The organic layer was separated, and the aqueous layer was extracted with

dichloromethane (2x50ml). The combined organic extracts were dried over magnesium sulfate. The solvent was evaporated *in vacuo* to give the title compound as a light yellowish solid (15.92g, 95%). ES-MS (M+H)⁺ = 214.

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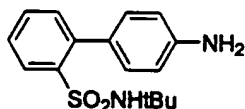
Example 4



To a solution of the compound of example 3 (15.92g, 74.7mmol) in tetrahydrofuran (200ml) in an ice bath was added 1.6M n-butyllithium in hexane (100ml, 164mmol) dropwise over 30 minutes. The mixture remained a clear solution. In an ice bath it was added triisopropylborate (24.1ml, 104mmol) dropwise. The mixture was stirred at room temperature for 3.5hrs, solution becoming cloudy. After it was cooled in an ice bath, 1N hydrochloride (200ml) was added. The mixture was stirred at room temperature overnight. It was extracted with ether (2x50ml). The organic extract was washed with 1N sodium hydroxide (2x60ml). The aqueous solution was acidified to pH=1 with 6N hydrochloride, and then extracted with ether (2x100ml). The ether extract was dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was recrystallized by ether and hexane to give the title compound as a white solid (11.5g, 60%). ES-MS (M+H)⁺ = 258.

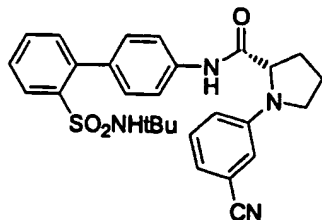
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Example 5

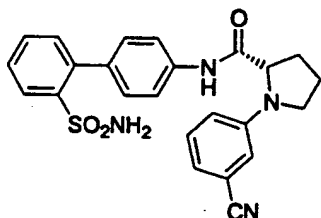


To a solution of the compound of example 4 (6.4g, 25mmol) in toluene (120ml) was added water (15ml), 5N sodium hydroxide (40ml), isopropanol (60ml), 4-bromoaniline (8.57g, 50mmol) and tetrakis(triphenylphosphine)palladium (0) (1.44g, 1.25mmol). The mixture was refluxed for 6 hrs, cooled to room temperature, and diluted with ethyl acetate. The organic layer was washed with water (50ml), and dried over magnesium sulfate. After the evaporation of the solvent *in vacuo*, the crude residue was purified by silica gel chromatography using solvent system 30% ethyl acetate in hexane as eluent to give the title compound as a light yellowish solid (5g, 66%). ES-MS (M+H)⁺ = 305.

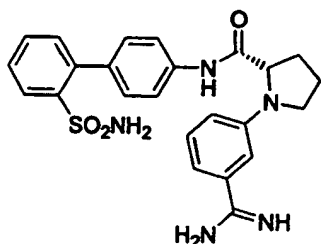
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Example 6

To a solution of the compound of example 2 (216mg, 1mmol) in dimethylformamide
5 (5ml) was added triethylamine (279ul, 2mmol), the compound of example 5 (304mg, 1mmol) and the coupling reagent BOP (531mg, 1.2mmol). The mixture was stirred at room temperature overnight. After the evaporation of the solvent *in vacuo*, the crude product was purified by silica gel column chromatography using solvent system 30-50% ethyl acetate in hexane as eluent to give the title compound as an oil
10 (220mg, 44%). ES-MS (M+H)⁺ = 503.

Example 7

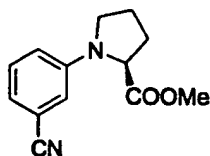
15 The compound of example 6 (220mg, 0,44mmol) was dissolved in trifluoroacetic acid (3ml). The mixture was refluxed for 1.5hrs. The solvent was evaporated *in vacuo* to give the title compound as an oil (200mg, 100%). MS-ES (M+H)⁺ = 447.

Example 8

A solution of the compound of example 7 (200mg, 0.44mmol), hydroxylamine hydrochloride (76mg, 1.1mmol) and triethylamine (153ul, 1.1mmol) in absolute

- ethanol (3ml) was stirred at 40 °C for 15 hrs. After the evaporation of the solvent *in vacuo*, the residue was dissolved in acetic acid (2ml), and acetic anhydride (83ul, 0,88mmol) was added. The mixture was stirred at room temperature for 3 hrs. It was diluted with absolute methanol (5ml), and 10% Pd/C (catalytic amount) was added.
- 5 The mixture was applied with 50psi hydrogen for 6 hrs. After the filtration through Celite to remove the catalyst, the filtrate was concentrated *in vacuo*. The crude residue was purified by RP-HPLC to give the title compound as a white powder (89mg, 46%). ES-MS (M+H)+ = 464.

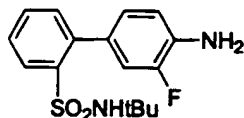
10 Example 9



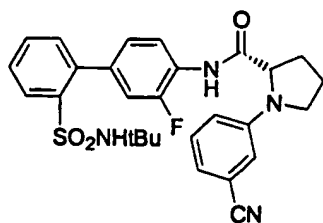
- To a solution of the compound of example 2 (210mg, 1mmol) in methanol (5ml) in an ice bath was added thionyl chloride (142ul, 2mmol) dropwise. The mixture was stirred at room temperature overnight. After the concentration *in vacuo*, it was dissolved in dichloromethane (10ml), and washed with water (5ml). The organic extract was dried over magnesium sulfate, and concentrated *in vacuo* to give the title compound as an oil (290mg, 100%). ES-MS (M+H)+ = 231.
- 15

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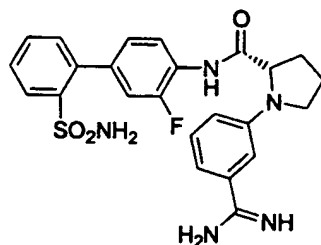
Example 10



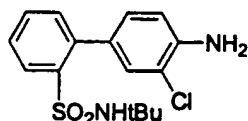
- To a solution of the compound of example 4 (2.06g, 8mmol) in toluene (60ml) was added water (4ml), 8N sodium hydroxide (8ml), isopropanol (16ml), 2-fluoro-4-iodoaniline (3.8g, 16mmol) and tetrakis(triphenylphosphine)palladium (0) (464mg, 0.4mmol). The mixture was refluxed for 3-4 hrs, cooled to room temperature, and diluted with ethyl acetate. The organic layer was washed with water (25ml), and dried over magnesium sulfate. After the evaporation of the solvent *in vacuo*, the crude residue was purified by silica gel column chromatography using solvent system 20-30% ethyl acetate in hexane as eluent to give the title compound as a white solid (1.49g, 58%). ES-MS (M+H)+ = 323.
- 25
- 30

Example 11

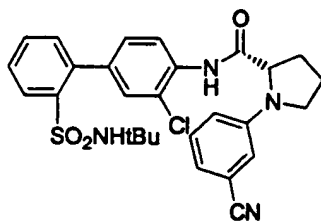
To a solution of the compound of example 10 (110mg, 0.34mmol) in
5 dichloromethane (5ml) was added 2.0M trimethylaluminum in hexane (0.51ml,
1.02mmol). The mixture was stirred at room temperature for 30 minutes, methane
gas evolved. A solution of the compound of example 9 (78mg, 0.34mmol) in
dichloromethane (1ml) was added. The mixture was stirred at room temperature
overnight. 1N hydrochloride was added to acidify the solution to pH=2. After the
10 addition of water and dichloromethane, the organic layer was separated, and the
aqueous layer was extracted with dichloromethane. The combined organic extracts
were dried over magnesium sulfate, and concentrated *in vacuo*. The crude residue
was purified by silica gel column chromatography using solvent system 25% ethyl
acetate in hexane as eluent to give the title compound as a solid (90mg, 51%). ES-
15 MS (M+H)⁺ = 521.

Example 12

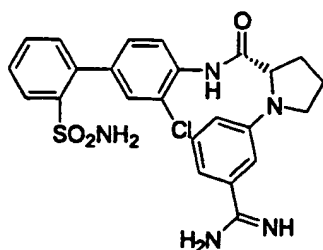
20 To a solution of the compound of example 11 (90mg, 0.17mmol) in absolute
methanol (3ml) in an ice bath was saturated with hydrochloride gas for 10 minutes.
The mixture was stirred at room temperature for 3 hrs. After the evaporation of the
solvent *in vacuo*, the residue was dissolved in absolute methanol (3ml), and
25 ammonia acetate (80mg, 1.04mmol) was added. The mixture was refluxed for 3 hrs.
The solvent was evaporated *in vacuo*. The crude residue was purified by RP-HPLC
to give the title compound as a white powder (36mg, 44%). ES-MS (M+H)⁺ = 482.

Example 13

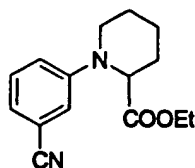
To a solution of the compound of example 4 (2.06g, 8mmol) in toluene (60ml) was added water (4ml), 8N sodium hydroxide (8ml), isopropanol (16ml), 2-chloro-4-iodoaniline (4.06g, 16mmol) and tetrakis(triphenylphosphine)palladium(0) (464mg, 0.4mmol). The mixture was refluxed for 3-4 hrs, cooled to room temperature, and diluted with ethyl acetate. The organic layer was washed with water (25ml), and dried over magnesium sulfate. After the evaporation of the solvent *in vacuo*, the crude residue was purified by silica gel column chromatography using solvent system 20-30% ethyl acetate in hexane as eluent to give the title compound as a white solid (1.43g, 53%). ES-MS (M+H)+ = 339.

Example 14

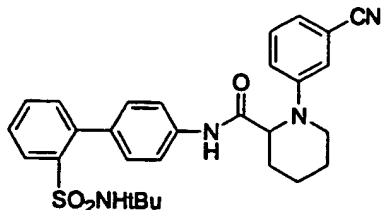
To a solution of the compound of example 13 (147mg, 0.43mmol) in dichloromethane (5ml) was added 2.0M trimethylaluminum in hexane (0.65ml, 1.30mmol). The mixture was stirred at room temperature for 30 minutes, methane gas evolved. A solution of the compound of example 9 (100mg, 0.43mmol) in dichloromethane (1ml) was added. The mixture was stirred at room temperature overnight. 1N hydrochloride was added to acidify the solution to pH=2. After the addition of water and dichloromethane, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give the title compound as a solid (180mg, 78%). ES-MS (M+H)+ = 537.

Example 15

To a solution of the compound of example 14 (180mg, 0.34mmol) in absolute
5 methanol (3ml) in an ice bath was saturated with hydrochloride gas for 10 minutes.
The mixture was stirred at room temperature for 3 hrs. After the evaporation of the
solvent *in vacuo*, the residue was dissolved in absolute methanol (3ml), and
ammonia acetate (155mg, 2mmol) was added. The mixture was refluxed for 3 hrs.
The solvent was evaporated *in vacuo*. The crude residue was purified by RP-HPLC
10 to give the title compound as a white powder (55mg, 33%). ES-MS (M+H)⁺ = 498.

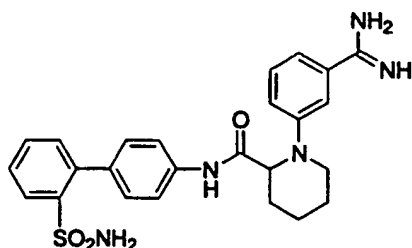
Example 16

To a solution of 3-bromobenzonitrile (1.82g, 10mmol), ethyl pipercolinate (3.14g,
15 20mmol), sodium tert-butoxide (1.35g, 14mmol) and (s)-(-)-2,2'-bis
(diphenylphosphino)-1,1'-binaphthyl (125mg, 0.2mmol) in toluene (20ml) was
added tris(dibenzylideneacetone)dipalladium (0) (92mg, 0.1mmol). The mixture was
stirred at 90 °C for 6 hrs. After the filtration of the solid, the filtrate was concentrated
in vacuo. The residue was purified by silica gel column chromatography using
20 solvent system 5-10% ethyl acetate in hexane as eluent to give the title compound as
an oil (770mg, 30%). ES-MS (M+H)⁺ = 259.

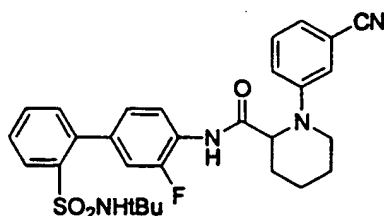
Example 17

To a solution of the compound of example 5 (189mg, 0.62mmol) in dichloromethane (2ml) was added 2.0M trimethylaluminum in hexane (0.93ml, 1.86mmol). The mixture was stirred at room temperature for 30 minutes, methane gas evolved. A solution of the compound of example 16 (160mg, 0.62mmol) in dichloromethane (1ml) was added. The mixture was stirred at room temperature overnight. 1N hydrochloride was added to acidify the solution to pH=2. After the addition of water and dichloromethane, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, and concentrated *in vacuo* to give the title compound as a yellow solid (330mg, 100%). ES-MS (M+H)⁺ = 517.

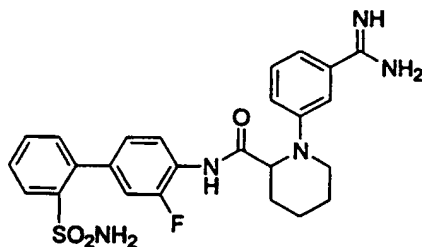
Example 18



A solution of the compound of example 17 (330mg, 0.64mmol), hydroxylamine hydrochloride (110mg, 1.6mmol) and triethylamine (223ul, 1.6mmol) in absolute ethanol (10ml) was stirred at 40 °C for 15 hrs. After the evaporation of the solvent *in vacuo*, the residue was dissolved in acetic acid (4ml), and acetic anhydride (121ul, 1.28mmol) was added. The mixture was stirred at room temperature for 3 hrs. It was diluted with absolute methanol (7ml), and 10% Pd/C (catalytic amount) was added. The mixture was applied with 50psi hydrogen for 6 hrs. After the filtration through Celite to remove the catalyst, the filtrate was concentrated *in vacuo*. The residue was dissolved in trifluoroacetic acid (5ml). The mixture was refluxed for 1.5hrs. After the evaporation of the solvent *in vacuo*, the crude residue was purified by RP-HPLC to give the title compound as a white powder (200mg, 62%). ES-MS (M+H)⁺ = 478.

Example 19

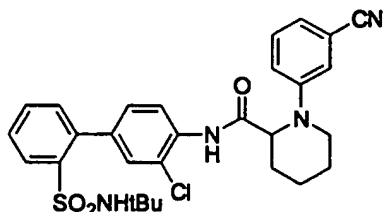
To a solution of the compound of example 10 (125mg, 0.39mmol) in
5 dichloromethane (5ml) was added 2.0M trimethylaluminum in hexane (0.58ml, 1.16mmol). The mixture was stirred at room temperature for 30 minutes, methane gas evolved. A solution of the compound of example 16 (100mg, 0.39mmol) in dichloromethane (1ml) was added. The mixture was stirred at room temperature overnight. 1N hydrochloride was added to acidify the solution to pH=2. After the
10 addition of water and dichloromethane, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography using solvent system 20% ethyl acetate in hexane as eluent to give the title compound as a solid (150mg, 72%). ES-
15 MS (M+H)⁺ = 535.

Example 20

20 To a solution of the compound of example 19 (100mg, 0.19mmol) and triethylamine (1ml) in absolute pyridine (10ml) was saturated with hydrosulfide gas for 10minutes. The mixture was stirred at room temperature for 15 hrs. After the evaporation of the solvent *in vacuo*, the green residue was dissolved in acetone (10ml). Iodomethane
25 (118ul, 1.9mmol) was added. The mixture was refluxed for 1hr. After the evaporation of the solvent *in vacuo*, the residue was dissolved in absolute methanol (15ml), and ammonia acetate (176mg, 3.28mmol) was added. The mixture was refluxed for 3 hrs. After the concentration *in vacuo*, the residue was dissolved in trifluoroacetic acid (5ml), and was refluxed for 1hr. The solvent was evaporated *in*

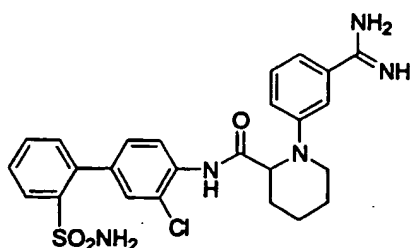
vacuo. The crude residue was purified by RP-HPLC to give the title compound as a white powder. ES-MS (M+H)⁺ = 496.

5 Example 21



To a solution of the compound of example 13 (132mg, 0.39mmol) in dichloromethane (5ml) was added 2.0M trimethylaluminum in hexane (0.58ml, 1.17mmol). The mixture was stirred at room temperature for 30 minutes, methane gas evolved. A solution of the compound of example 16 (100mg, 0.39mmol) in dichloromethane (1ml) was added. The mixture was stirred at room temperature overnight. 1N hydrochloride solution was added to acidify the solution to pH=2. After the addition of water and dichloromethane, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography using solvent system 20% ethyl acetate in hexane as eluent to give the title compound as an oil (160mg, 75%). ES-MS (M+H)⁺ = 551.

Example 22



To a solution of the compound of example 21 (100mg, 0.18mmol) and triethylamine (1ml) in absolute pyridine (10ml) was saturated with hydrosulfide gas for 10 minutes. The mixture was stirred at room temperature for 15 hrs. After the evaporation of the solvent *in vacuo*, the green residue was dissolved in acetone (10ml). Iodomethane (112ul, 1.8mmol) was added. The mixture was refluxed for 1hr. After the

evaporation of the solvent *in vacuo*, the residue was dissolved in absolute methanol (15ml), and ammonia acetate (166mg, 2.16mmol) was added. The mixture was refluxed for 3 hrs. After the evaporation of the solvent *in vacuo*, the residue was dissolved in trifluoroacetic acid (5ml), and was refluxed for 1hr. The solvent was
5 evaporated *in vacuo*. The crude residue was purified by RP-HPLC to give the title compound as a white powder. ES-MS (M+H)⁺ = 512.

BIOLOGICAL ACTIVITY EXAMPLES

Evaluation of the compounds of this invention is guided by *in vitro* protease
10 activity assays (see below) and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters.

The compounds of the present invention are dissolved in buffer to give solutions containing concentrations such that assay concentrations range from 0 to 100 μ M. In the assays for thrombin, prothrombinase and factor Xa, a synthetic
15 chromogenic substrate is added to a solution containing test compound and the enzyme of interest and the residual catalytic activity of that enzyme is determined spectrophotometrically. The IC₅₀ of a compound is determined from the substrate turnover. The IC₅₀ is the concentration of test compound giving 50% inhibition of the substrate turnover. The compounds of the present invention desirably have an
20 IC₅₀ of less than 500 nM in the factor Xa assay, preferably less than 200 nM, and more preferred compounds have an IC₅₀ of about 100 nM or less in the factor Xa assay. The compounds of the present invention desirably have an IC₅₀ of less than 4.0 μ M in the prothrombinase assay, preferably less than 200 nM, and more preferred compounds have an IC₅₀ of about 10 nM or less in the prothrombinase
25 assay. The compounds of the present Invention desirably have an IC₅₀ of greater than 1.0 μ M in the thrombin assay, preferably greater than 10.0 μ M, and more preferred compounds have an IC₅₀ of greater than 100.0 μ M in the thrombin assay.

Amidolytic Assays for determining protease inhibition activity

The factor Xa and thrombin assays are performed at room temperature, in 0.02 M Tris-HCl buffer, pH 7.5, containing 0.15 M NaCl. The rates of hydrolysis of the para-nitroanilide substrate S-2765 (Chromogenix) for factor Xa, and the
5 substrate Chromozym TH (Boehringer Mannheim) for thrombin following preincubation of the enzyme with inhibitor for 5 minutes at room temperature, and were determined using the Softmax 96-well plate reader (Molecular Devices), monitored at 405 nm to measure the time dependent appearance of p-nitroaniline.

The prothrombinase inhibition assay is performed in a plasma free system
10 with modifications to the method described by Sinha, U. *et al.*, *Thromb. Res.*, 75, 427-436 (1994). Specifically, the activity of the prothrombinase complex is determined by measuring the time course of thrombin generation using the p-nitroanilide substrate Chromozym TH. The assay consists of preincubation (5 minutes) of selected compounds to be tested as inhibitors with the complex formed
15 from factor Xa (0.5 nM), factor Va (2 nM), phosphatidyl serine:phosphatidyl choline (25:75, 20 μ M) in 20 mM Tris-HCl buffer, pH 7.5, containing 0.15 M NaCl, 5 mM CaCl₂ and 0.1% bovine serum albumin. Aliquots from the complex-inhibitor mixture are added to prothrombin (1 nM) and Chromozym TH (0.1 mM). The rate of substrate cleavage is monitored at 405 nm for two minutes. Eight different
20 concentrations of inhibitor are assayed in duplicate. A standard curve of thrombin generation by an equivalent amount of untreated complex are used for determination of percent inhibition.

Antithrombotic Efficacy in a Rabbit Model of Venous Thrombosis

25 A rabbit deep vein thrombosis model as described by Hollenbach, S. *et al.*, *Thromb. Haemost.* 71, 357-362 (1994), is used to determine the in-vivo antithrombotic activity of the test compounds. Rabbits are anesthetized with I.M. injections of Ketamine,

Xylazine, and Acepromazine cocktail. A standardized protocol consists of insertion of a thrombogenic cotton thread and copper wire apparatus into the abdominal vena cava of the anesthetized rabbit. A non-occlusive thrombus is allowed to develop in the central venous circulation and inhibition of thrombus growth is used as a measure of the antithrombotic activity of the studied compounds. Test agents or control saline are administered through a marginal ear vein catheter. A femoral vein catheter is used for blood sampling prior to and during steady state infusion of test compound. Initiation of thrombus formation begins immediately after advancement of the cotton thread apparatus into the central venous circulation. Test compounds are administered from time = 30 min to time = 150 min at which the experiment is terminated. The rabbits are euthanized and the thrombus excised by surgical dissection and characterized by weight and histology. Blood samples are analyzed for changes in hematological and coagulation parameters.

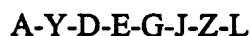
Effects of Compounds in Rabbit Venous Thrombosis model

Administration of compounds in the rabbit venous thrombosis model demonstrates antithrombotic efficacy at the higher doses evaluated. There are no significant effects of the compound on the aPTT and PT prolongation with the highest dose (100 $\mu\text{g/kg}$ + 2.57 $\mu\text{g/kg/min}$). Compounds have no significant effects on hematological parameters as compared to saline controls. All measurements are an average of all samples after steady state administration of vehicle or (D)-Arg-Gly-Arg-thiazole. Values are expressed as mean \pm SD.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods.

WHAT IS CLAIMED IS:

1. A compound according to the formula I:



5 wherein:

A is selected from:

- (a) C₁-C₆-alkyl;
- (b) C₃-C₈-cycloalkyl;
- 10 (g) -NR₂R₃, R₃C(=NR₂)-, R₂R₃N-C(=NR₂)-, R₂R₃N-C(=NR₂)-N(R₃)-
- (c) phenyl, which is independently substituted with 0-2 R¹ substituents;
- (d) naphthyl, which is independently substituted with 0-2 R¹ substituents; and
- (e) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R¹ substituents;

R¹ is selected from:

- Halo, R₂-C(=NR₃)-, R₂R₃N-C(=NR₂)-, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, (CH₂)_mNR²R³, SO₂NR²R³, SO₂R², CF₃, OR², and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C₁-C₄-alkyl, -CN, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl and -NO₂;

R² and R³ are independently selected from the group consisting of:

- H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl,

C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

m is an integer of 0-2;

Y is a member selected from the group consisting of:

- 5 a direct link, -CH₂-, -C(=O)-, -N(R⁴)-, -N(R⁴)CH₂-, -C=N(R⁴)-, -C(=O)-N(R⁴)-, -N(R⁴)-C(=O)-, -SO₂-, -O-, -SO₂-N(R⁴)- and -N(R⁴)-SO₂-;

R⁴ is selected from:

- 10 H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

D is a direct link or is a member selected from the group consisting of:

- 15 (a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;
- (b) naphthyl, which is independently substituted with 0-2 R^{1a} substituents;
- and
- (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;
- 20

R^{1a} is selected from:

- 25 Halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, (CH₂)_mNR^{2a}R^{3a}, SO₂NR^{2a}R^{3a}, SO₂R^{2a}, CF₃, OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

R^{2a} and R^{3a} are independently selected from the group consisting of:

5 H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

E is a member selected from the group consisting of:

10 -N(R⁵)-C(=O)-, -C(=O)-N(R⁵)-, -N(R⁵)-C(=O)-N(R⁶)-, -SO₂-N(R⁵)-, -N(R⁵)-SO₂-N(R⁶)- and -N(R⁵)-SO₂-N(R⁶)-C(=O)-;

R⁵ and R⁶ are independently selected from:

15 H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl, C₀₋₄alkylnaphthyl, C₀₋₄alkylheteroaryl, C₁₋₄alkylCOOH and C₁₋₄alkylCOOC₁₋₄alkyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl, naphthyl and heteroaryl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

G is a member selected from the group consisting of from:

20 a direct link, -CR⁷R⁸- and -CR^{7a}R^{8a}-CR^{7b}R^{8b}-

wherein R⁷, R⁸, R^{7a}, R^{8a}, R^{7b} and R^{8b} are independently a member selected from from the group consisting of:

25 hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkyl-C₃₋₈cycloalkyl, C₀₋₄alkylphenyl, C₀₋₄alkylnaphthyl, -OR⁹, -C₀₋₄alkylCOOR⁹, -C₀₋₄alkylC(=O)NR⁹R¹⁰, -C₀₋₄alkylC(=O)NR⁹-CH₂-CH₂-O-R¹⁰, -C₀₋₄alkylC(=O)NR⁹(-CH₂-CH₂-O-R¹⁰)₂, -N(R⁹)COR¹⁰, -N(R⁹)C(=O)R¹⁰, -N(R⁹)SO₂R¹⁰, and a naturally occurring or synthetic amino acid side chain, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkyl-C₃₋₈cycloalkyl, -CN and -NO₂;

30

R^9 and R^{10} are independently selected from:

- 5 H, C_{1-4} alkyl, C_{0-4} alkylphenyl and C_{0-4} alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl- C_{3-8} cycloalkyl, -CN and -NO₂, and wherein R^9 and R^{10} taken together can form a 5-8 membered heterocyclic ring;

J is a member selected from the group consisting of:



10

wherein the ring carbons or the second ring nitrogen of the amino ring structure and/or the ring carbons on the alkylene bridging groups attached to the amino ring structure may be independently substituted by a total of 0 to 4 R^{11} , R^{11a} , R^{11b} and R^{11c} groups;

- 15 R^{11} , R^{11a} , R^{11b} and R^{11c} are independently a member selected from the group consisting of:

- 20 hydrogen, -OH, -O- C_{1-4} alkyl, - C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{0-4} alkyl- C_{3-8} cycloalkyl, C_{0-4} alkylphenyl, C_{0-4} alkylnaphthyl, C_{0-4} alkylheterocyclic ring having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S, CH_2COOC_{1-4} alkyl, CH_2COOC_{1-4} alkylphenyl and CH_2COOC_{1-4} alkylnaphthyl;

Z is a member selected from the group consisting of:

- (a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;
- (b) naphthyl, which is independently substituted with 0-2 R^{1b} substituents;
- 25 and
- (c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected

from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

5 Halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, -NO₂, NR^{2b}R^{3b}, SO₂NR^{2b}R^{3b}, SO₂R^{2b}, CF₃, OR^{2b}, O-CH₂-CH₂-OR^{2b}, O-CH₂-COOR^{2b}, N(R^{2b})-CH₂-CH₂-OR^{2b}, N(-CH₂-CH₂-OR^{2b})₂, N(R^{2b})-C(=O)R^{3b}, N(R^{2b})-SO₂-R^{3b}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be
10 independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

R^{2b} and R^{3b} are independently selected from the group consisting of:

15 H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN and -NO₂;

20 L is selected from:

H, -CN, C(=O)NR¹²R¹³, (CH₂)_nNR¹²R¹³, C(=NR¹²)NR¹²R¹³, NR¹²R¹³, OR¹², -NR¹²C(=NR¹²)NR¹²R¹³, and NR¹²C(=NR¹²)-R¹³;

R¹² and R¹³ are independently selected from:

25 hydrogen, -OR¹⁴, -NR¹⁴R¹⁵, C₁₋₄alkyl, C₀₋₄alkylphenyl, C₀₋₄alkylnaphthyl, COOC₁₋₄alkyl, COO-C₀₋₄alkylphenyl and COO-C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

30 R¹⁴ and R¹⁵ are independently selected from:

H, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, C₀₋₄alkylphenyl and C₀₋₄alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkylC₃₋₈cycloalkyl, -CN, and -NO₂;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

2. A compound of claim 1, wherein:

A is selected from:

(a) -NR²R³, R³C(=NR²)-, R²R³N-C(=NR²)-, R²R³N-C(=NR²)-N(R³)-

(b) phenyl, which is independently substituted with 0-2 R¹ substituents;

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R¹ substituents;

R¹ is selected from:

halo, R²-C(=NR³)-, R²R³N-C(=NR²)-, C₁₋₄alkyl, NO₂, -CN, (CH₂)_mNR²R³, CONR²R³, SO₂NR²R³, SO₂R², CF₃, OR², and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S;

R² and R³ are independently selected from the group consisting of:

H, C₁₋₄alkyl and C₀₋₄alkylaryl,

m is an integer of 0-2;

Y is a member selected from the group consisting of:

a direct link, -CH₂-, -C(=O)-, -N(R⁴)-, -N(R⁴)CH₂-, and -C=N(R⁴)-,

R⁴ is selected from:

H, C₁₋₄alkyl and C₀₋₄alkylaryl;

D is absent or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substituents; and

5 (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

R^{1a} is selected from:

10 Halo, C₁₋₄alkyl, -CN, -NO₂, (CH₂)_mNR^{2a}R^{3a}, SO₂NR^{2a}R^{3a}, SO₂R^{2a}, CF₃, OR^{2a}, and a 5-6 membered aromatic heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C₁₋₄alkyl and C₀₋₄alkylaryl;

E is a member selected from the group consisting of:

15 -N(R⁵)-C(=O)-, and -C(=O)-N(R⁵)-,

R⁵ and R⁶ are independently selected from:

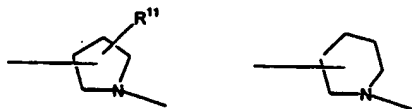
H, C₁₋₄alkyl, C₀₋₄alkylaryl, C₀₋₄alkylheteroaryl, C₁₋₄alkylCOOH and C₁₋₄alkylCOOC₁₋₄alkyl;

G is a member selected from the group consisting of:

20 a direct link,

J is a member selected from the group consisting of:

wherein the ring carbons or the second ring nitrogen of the amino ring structure



and/or the ring carbons on the alkylene bridging groups attached to the amino ring structure may be independently substituted by a total of 0 to 4 R¹¹, R^{11a}, R^{11b} and R^{11c} groups;

25

R¹¹, R^{11a}, R^{11b} and R^{11c} are independently a member selected from the group consisting of:

- hydrogen, -OH, -O-C₁₋₄alkyl, -C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₀₋₄alkyl-C₃₋₈cycloalkyl, C₀₋₄alkylphenyl, C₀₋₄alkylnaphthyl, C₀₋₄alkylheterocyclic ring having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S, CH₂COOC₁₋₄alkyl, CH₂COOC₁₋₄alkylphenyl and CH₂COOC₁₋₄alkylnaphthyl;

Z is a member selected from the group consisting of:

- (a) aryl, which is independently substituted with 0-2 R^{1b} substituents; and
- (b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

- halo, C₁₋₄alkyl, -CN, -NO₂, NR^{2b}R^{3b}, SO₂NR^{2b}R^{3b}, SO₂R^{2b}, CF₃, OR^{2b}, O-CH₂-CH₂-OR^{2b}, O-CH₂-COOR^{2b}, N(R^{2b})-CH₂-CH₂-OR^{2b}, N(-CH₂-CH₂-OR^{2b})₂, N(R^{2b})-C(=O)R^{3b}, N(R^{2b})-SO₂-R^{3b}, and a 5-6 membered aromatic heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S;

R^{2b} and R^{3b} are independently selected from the group consisting of:

H, C₁₋₄alkyl and C₀₋₄alkylaryl;

L is selected from:

- H, -CN, C(=O)NR¹²R¹³, (CH₂)_nNR¹²R¹³, C(=NR¹²)NR¹²R¹³, NR¹²R¹³, OR¹², -NR¹²C(=NR¹²)NR¹²R¹³ and NR¹²C(=NR¹²)-R¹³;

R¹² and R¹³ are independently selected from:

hydrogen, -OR¹⁴, -NR¹⁴R¹⁵, C₁₋₄alkyl, C₀₋₄alkylaryl, COOC₁₋₄alkyl, and COO-C₀₋₄alkylaryl; and

- R¹⁴ and R¹⁵ are independently selected from:

H and C₁₋₄alkyl.

3. A compound of claim 1, wherein:

A is selected from:

(a) phenyl, which is independently substituted with 0-2 R^1 substituents;

(b) $-NR_2R_3$, $R_3C(=NR_2)-$, $R_2R_3N-C(=NR_2)-$, $R_2R_3N-C(=NR_2)-N(R_3)-$
5 and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^1 substituents;

10 R^1 is selected from:

halo, $R_2-C(=NR_3)-$, $R_2R_3N-C(=NR_2)-$, $(CH_2)_mNR^2R^3$, $SO_2NR^2R^3$ and SO_2R^2 ;

R^2 and R^3 are independently selected from the group consisting of:

H and C_{1-4} alkyl;

15 Y is a member selected from the group consisting of:

a direct link, $-C(=O)-$, CH_2 , $C(=NH)-$;

D is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substituents; and

(b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;
20

R^{1a} is selected from:

Halo and C_{1-4} alkyl;

25 R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C_{1-4} alkyl, C_{6-4} alkylaryl;

E is a member selected from the group consisting of:



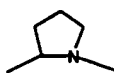
R^5 and R^6 are independently selected from:

H, C_{1-4} alkyl, C_{0-4} alkylaryl and C_{0-4} alkylheteroaryl;

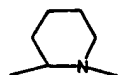
5 G is a member selected from the group consisting of:

a direct link,

J is a member selected from the group consisting of:



and



Z is a member selected from the group consisting of:

- 10 (a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;
- (b) an aromatic heterocyclic ring having from 5 to 10 ring atoms, wherein 1-4 ring atoms are selected from N, O and S, and wherein the ring may be substituted independently by from 0-2 R^{1b} substituents; and
- 15 (c) a fused aromatic bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, wherein the bicyclic ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

- 20 halo, C_{1-4} alkyl, OH, OBn, $O-CH_2-CH_2-OH$, $O-CH_2-CH_2-OCH_3$,
 $O-CH_2-COOH$, $O-CH_2-C(=O)-O-CH_3$, NH_2 , $NH-CH_2-CH_2-O-CH_3$,
 $NH-C(=O)-O-CH_3$, and $NH-SO_2-CH_3$;

L is selected from:



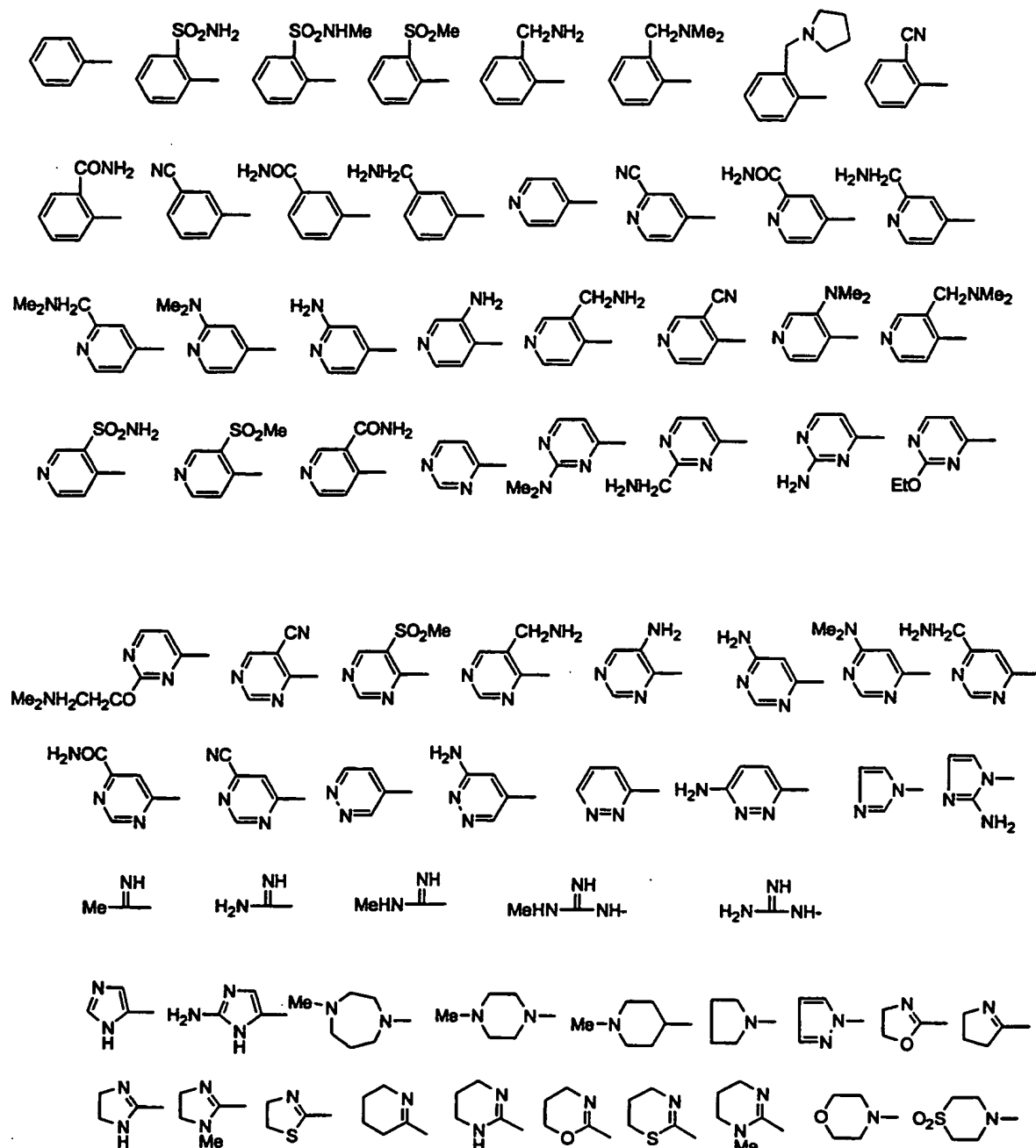
R^{12} and R^{13} are independently selected from:

hydrogen and C_{1-4} alkyl.

4. A compound of claim 1, wherein:

A is a member selected from the group consisting of:

5

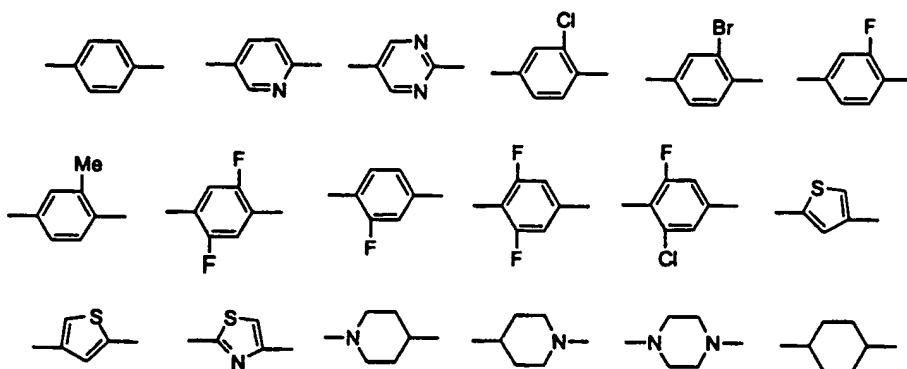


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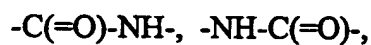
Y is selected from the group consisting of:

a direct link, $-CO-$, $-N(Me)-$, $-N(Me)-CH_2-$, CH_2- , $C(=NH)-$

D is a direct link or a member selected from the group consisting of:



5 E is a member selected from the group consisting of:

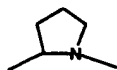


G is a member selected from the group consisting of:

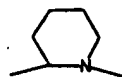
a direct link,

J is a member selected from the group consisting of:

10

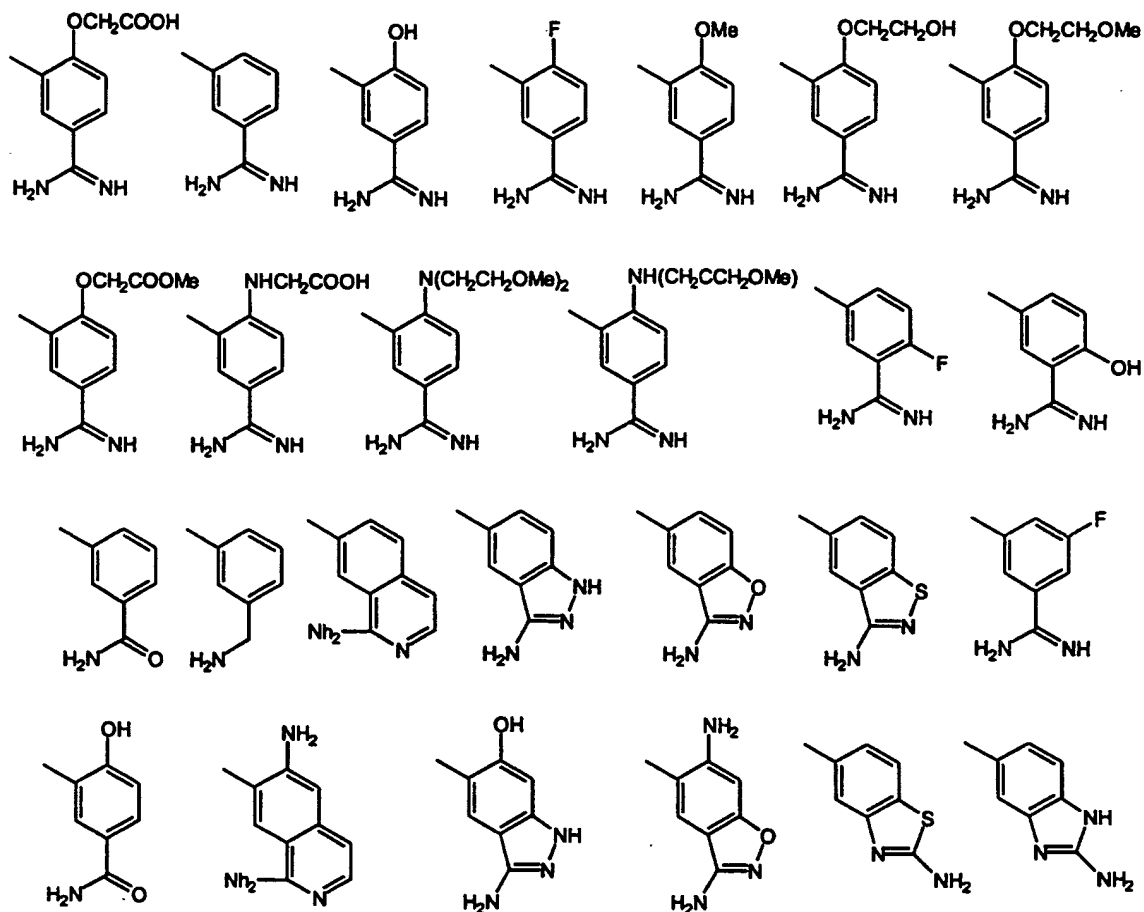


and



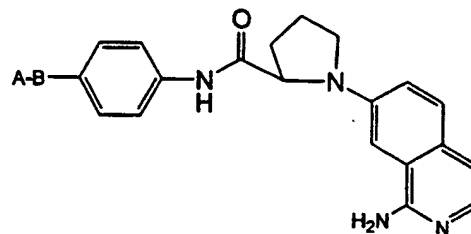
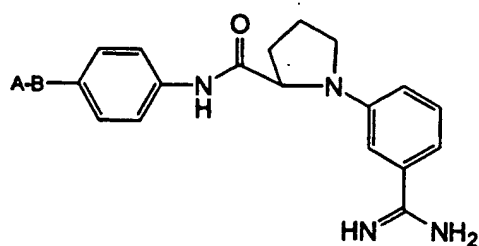
and

Z and L taken together are a member selected from the group consisting of:

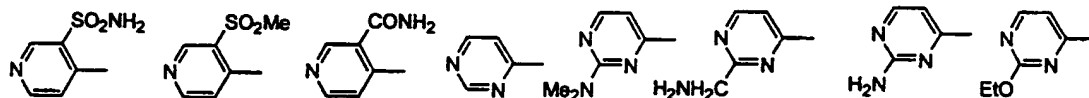
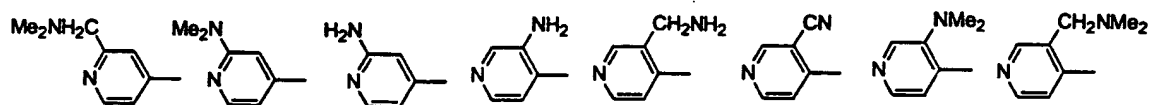
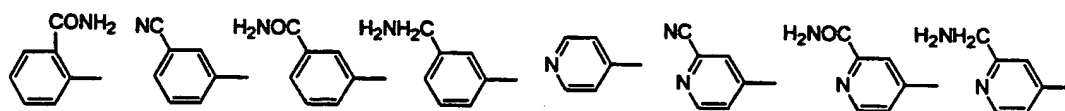
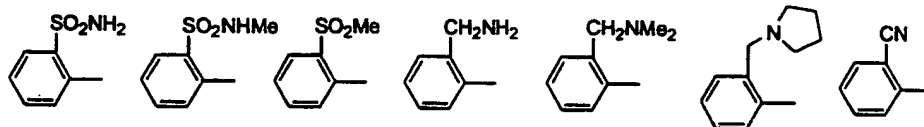


5. A compound of claim 1 selected from the group consisting of:

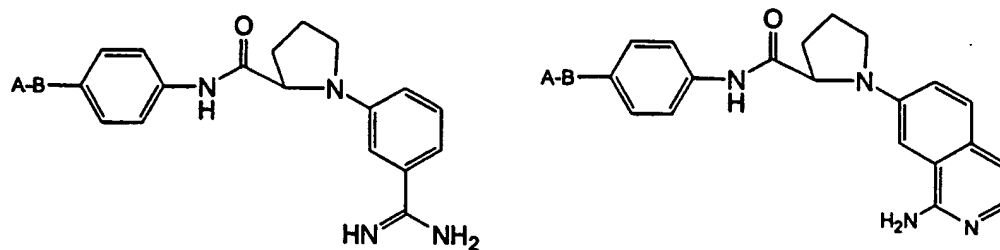
5



Where A-B is

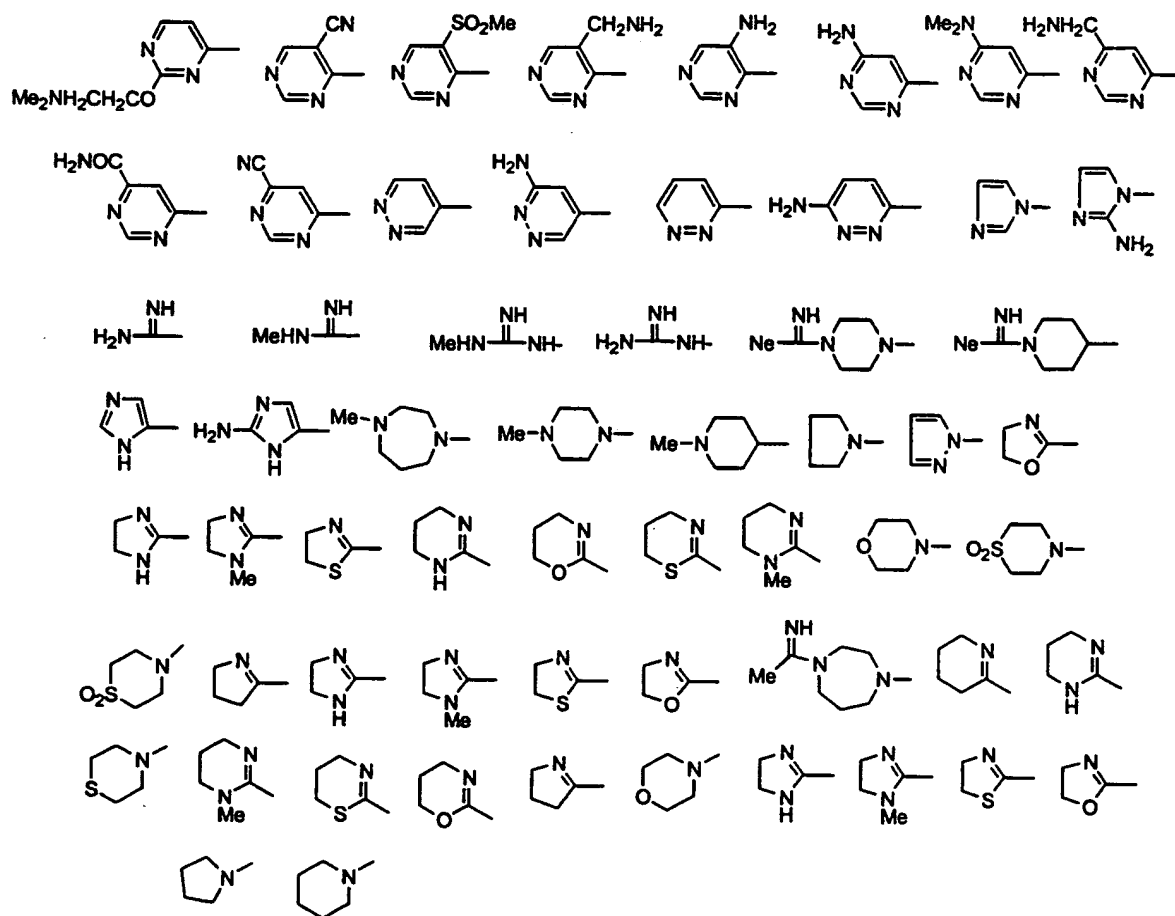


6. A compound of claim 1 selected from the group consisting of:

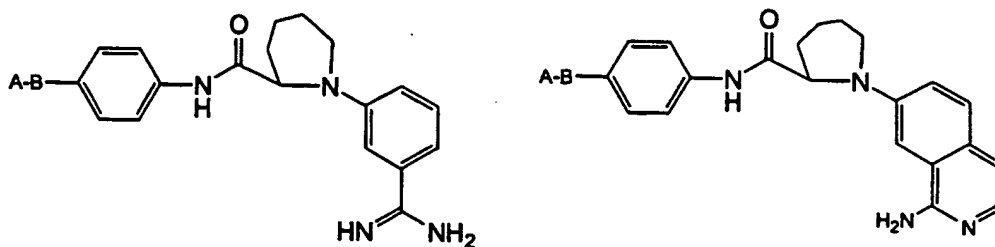


Where B is direct link, CH₂, -CO-, -SO₂-, -C(=NH)-, -NH-, -N(Me)-, -N(Me)CH₂-

A is selected from:

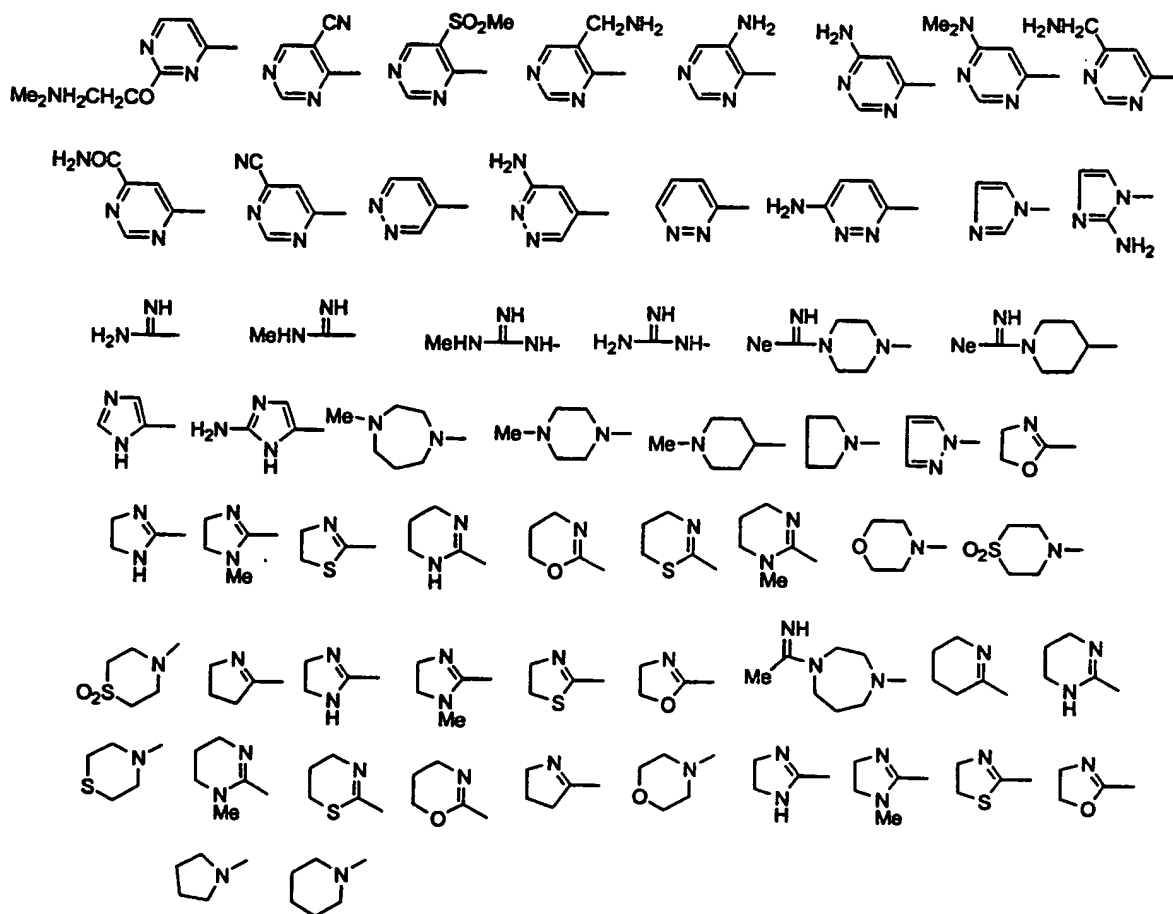


7. A compound of claim 1 selected from the group consisting of:

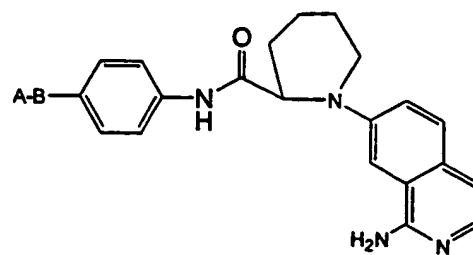
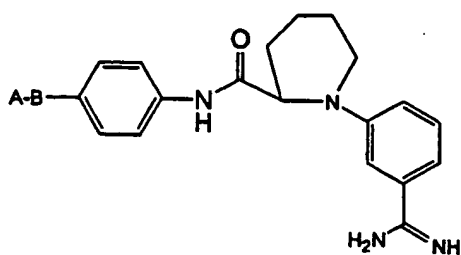


Where B is direct link, CH₂, -CO-, -SO₂, -C(=NH)-, -NH-, -N(Me)-, -N(Me)CH₂-

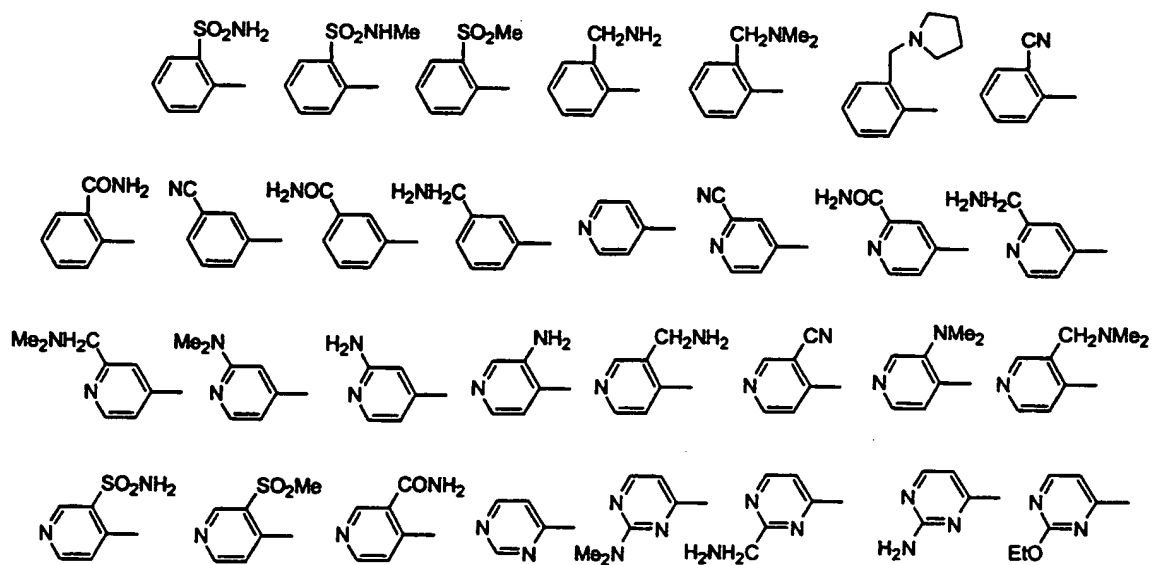
A is selected from:

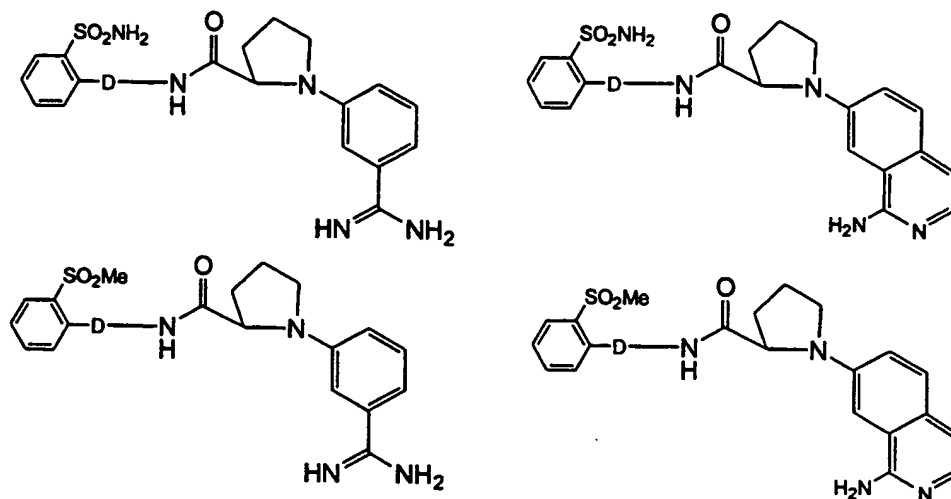


8. A compound of claim 1 selected from the group consisting of:



Where A-B is





Chemical structures of 15 different aromatic rings with substituents:

- 1,4-dimethylbenzene
- 1,4-dimethylpyridine
- 1,4-dimethylpyrimidine
- 1,3-dimethyl-4-chlorobenzene
- 1,3-dimethyl-4-bromobenzene
- 1,3-dimethyl-4-fluorobenzene
- 1,3-dimethyl-2-fluorobenzene
- 1,3-dimethyl-4-bromobenzene
- 1,3-dimethyl-4-chlorobenzene
- 1,3-dimethyl-2-fluorobenzene
- 1,3-dimethyl-4-fluorobenzene
- 1,3-dimethyl-2-fluorobenzene
- 1,3-dimethyl-4-fluorobenzene
- 1,3-dimethyl-2-fluorobenzene

10. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a compound of claim 1.
11. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a compound of claim 2.

12. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a compound of claim 3.
- 5 13. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising the step of administering to said mammal a therapeutically effective amount of a compound of claim 1.
- 10 14. The method of claim 13, wherein the condition is selected from the group consisting of: acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated
- 15 intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and
- 20 conditions requiring the fitting of prosthetic devices.
15. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising the step of administering to said mammal a therapeutically effective amount of a compound of claim 2.
- 25 16. The method of claim 15, wherein the condition is selected from the group consisting of: acute coronary syndrome, myocardial infarction, unstable angina,

refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated

5 intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and

10 conditions requiring the fitting of prosthetic devices.

17. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising the step of administering to said mammal a therapeutically effective amount of a compound of claim 3.

15

18. The method of claim 17, wherein the condition is selected from the group consisting of: acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome,

20 embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic

25 complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

19. A method for inhibiting the coagulation of biological samples, comprising the administration of a compound of claim 1.
20. A method for inhibiting the coagulation of biological samples, comprising
5 the administration of a compound of claim 2.